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hypochondrium are tender on pressure. During the second week the scab falls off and leaves in its place a punched-out ulcer, discharging a little pus. About the end of the second week, in an ordinary case, the patient perspires freely, and the temperature slowly returns to normal, while there is a general improvement in all the other symptoms. The appetite returns, slight diarrhœa occurs, the urine becomes more copious, and convalescence is now rapid; but the ulcer may take some weeks to heal entirely, and the glands in its immediate neighbourhood may continue to be painful.

In mild cases there may be no recognised constitutional symptoms; the fever is so trifling that the patient never keeps his bed, the eruption is absent or unnoticed, but the circumscribed necrosis of the skin and the glandular inflammation are always present. Such benign cases last only a week, but the average duration of a moderately severe attack is three weeks.

Complications.—The patient's life is endangered by the complications which may accompany or succeed a very serious attack, such as parotitis, melæna, coma, mania, cardiac weakness, and œdema of lungs. Bälz estimates the mortality at 15 per cent, while Tanaka considers it may sometimes be as high as 70 per cent.

The **treatment** must of course be symptomatic. Scheube, after many years' experience in Japan, points out that the Japanese react to antipyretics much more easily than Europeans.

F. M. SANDWITH.

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F. M. S.

PLAGUE

By J. F. Payne, M.D., F.R.C.P.

Bacteriology and Specific Treatment

By W. Bulloch, M.D., and Capt. S. R. Douglas, I.M.S.

Synonyms.—*Oriental plague*, *Bubonic plague*, *Pestis*, *Pestilentia*: *Pali plague* or *Mahamurrie* (in India). The *Black Death* (fourteenth century in Europe).

Definition.—An acute infective febrile disease, accompanied by inflammation of lymphatic glands, caused by a micro-organism, the *Bacillus pestis*.

History of the Plague.—The first historical notice of a disease like bubonic plague records its occurrence in Libya in the third century before Christ, or earlier; but this notice is only contained in a fragment from the writings of a much later physician, Rufus of Ephesus (about 100 A.D.), who also speaks of its occurrence in his own time in Libya, Egypt, and Syria. Whether it was clearly known to the classical Greek writers on medicine is doubtful, but Aretæus speaks of βουβῶνες λοιμώδεες, or pestilential buboes. The plague of Athens described by Thucydides was apparently not this disease; nor was the destructive pestilence in the reign of Marcus Aurelius alluded to by Galen. We meet with bubonic plague again, however, in the great Plague of Justinian, which started from Egypt 542 A.D., and spread over a large part of Europe; it was described in Gaul as *lues inguinaria*. Epidemics succeeded one another in this and the succeeding century. At the end of the seventh century bubonic plague prevailed in Italy and is unmistakably recorded by Bede in England. But after that time it is difficult to follow the track of plague. Many European pestilences are spoken of in mediæval histories, which may or may not have been bubonic plague, though no sufficiently clear record remains.

In the fourteenth century a new era began. All previous European plagues could be traced back, directly or remotely, to Africa, and for the most part to Egypt; but now a new epidemic invaded Europe from Asia by way of the Crimea and the Black Sea, its origin being referred to Cathay or China. This terrible pestilence, afterwards known as the "Death," or the "Black Death," appeared in Southern Italy in 1346-47, and made its way over the whole of Europe. It reached England early in 1348 and for several, probably five or six, years was prevalent in various parts of the country. Scotland and Ireland were affected in their turn; and no country in Europe seems to have escaped. A second epidemic occurred in 1361, and a third in 1368. The details of this great calamity have often been dwelt upon by historians, and cannot be

the old Levantine Plague seemed to have entirely vanished. It is clear, however, that in Asia Minor it did not die away, but only receded eastward. At the beginning of the nineteenth century, the Caucasus, according to Tholozan, was the centre from which epidemics radiated; but in the latter half of the century that centre was shifted to the mountains of Kurdistan.

Good authorities still held that the disease was probably not extinct; and these suspicions were confirmed by accounts received at Constantinople, in 1853, of an outbreak in the Azir district of Arabia: this outbreak has been followed by others at intervals of some years; the last was in 1889. In 1858 the same disease was heard of in Benghazi, where it must have prevailed at least two or three years before; and there it appeared again in 1874, and possibly again later. The plague has also recurred in the form of epidemics which were relics of the former wide distribution of plague along the whole northern coast of Africa, and in the province of Tripoli so lately as 1837.

The more recent accounts of plague in the Kurdistan district, on the frontiers of Turkey and Persia and Mesopotamia, begin with 1863; but this was not the first appearance of the disease in that part of the world—Baghdad and the neighbourhood had suffered severely at the beginning of that century, and for all we know to the contrary, for centuries before that. The chief known recent epidemics of Persia and Kurdistan were in 1863, in 1870-72, and in 1876-77; in 1877 a terrible epidemic occurred also in the town of Resht on the Caspian, which is an important occurrence in relation to the epidemic of 1878 on the Volga. The latest recorded appearance of plague in Persia was in 1885; but it was probably not the last. In Mesopotamia (Irak-Arabi), from 1856 onward for several years, there prevailed what is now known to have been the mild form of plague. In 1867 a definite epidemic was recorded; in 1873-74 another extending over a much wider area; and in 1876-77 one still more extensive, and very severe. A further outbreak occurred in 1880-81, which is said to have destroyed one-quarter or one-third of the population; and another in 1884.

The above short record is of interest as shewing how plague may extend its area in successive epidemics; and also as leading up to the comparatively small epidemic on the Volga in 1879, which caused so much alarm.

As has been shewn, in the years 1876 and 1877 the plague was very active. In June 1877, and also in the two years following, a febrile malady accompanied by buboes appeared in Astrakhan on the northern shore of the Caspian, a place in direct communication with Resht on the Persian shore, and it extended to neighbouring villages. Though it was of a mild type and caused but few deaths, it was certainly the mild or minor form of plague. In October 1878, a similar but more severe epidemic broke out in the Cossack settlement of Vetlanka, 130 miles up the Volga; and by December it assumed the character of the most virulent plague. The epidemic lasted in this village till 24th

epidemic occurred in the district of Kaochao, lying to the north of Pakhoi; and in the spring of 1894 it prevailed in towns to the south of Canton. From Canton to Hong Kong it was carried by the busy and continual traffic between the two places. It spread also to Macao, and other places on the coast, but not, it would seem, far inland in China. The mortality of Canton in 1894 is variously given from 40,000 to 100,000.

The Modern Period of Plague.—The extension of plague to the great seaport of Hong Kong has proved to be one of the most momentous events in the history of the disease. The first epidemic in Hong Kong lasted from May to August 1894, and caused a mortality of 3000. It has recurred, with a varying mortality, every year since, except 1895. The social conditions, filthy habits, with excessive overcrowding in small, dark, unventilated rooms generally situated over great warehouses swarming with rats, supplied a very favourable soil for the disease. But the most important point is that the communication of the port (as also that of Canton) by sea traffic with almost all parts of the world, has carried plague to seaports in India, Australia, Japan, Europe, Africa, and America, North and South. This general distribution has completely changed the aspect of a map shewing the parts of the world affected with plague, which has now become a "pandemic" and not merely a local epidemic disease. But its filiation is clearly traceable to the endemic centre of Yunnan in China.[1]

It was in Hong Kong that the *Bacillus pestis* was discovered by Kitasato, and later, but independently, by Yersin (*vide* p. 365). Passing over the nearer epidemic foci which were set up, we come to Bombay, where plague appeared early in 1896. Bombay, which had been free from plague for nearly 200 years, has an active trade with Hong Kong, and as the disease first appeared near the docks where the Chinese trade enters, and no other source of infection could be traced, it is almost certain that the infection came from China. The precise date and manner of conveyance of infection could not be traced, since the disease was as usual first overlooked; but before the outbreak among men was perceived, rats are known to have been dying in large numbers, so that it is most probable that rats conveyed in ships were the channel of infection. The disease was at first mild, and, as is usual in such cases, the diagnosis of plague was received with doubt or denial till, in October 1896, Haffkine's bacteriological investigations left no doubt on the matter. The disease spread from the dock-quarter to other parts of the city. Active preventive measures were taken but were hindered by the active resistance of the population. In February 1897 the highest mortality was reached. Nearly half the population left the city in a panic, carrying the infection to other parts, and since then, plague has never been absent from Bombay.

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[1] A map of the present distribution of plague is given in Dr. Simpson's "Treatise on Plague." Comparative maps shewing the distribution before and after 1894 were given in the *Quarterly Review*, Oct. 1901.

other port on the Persian Gulf. From Tamatave cases were carried to Lorenzo Marquez on the African coast, but no epidemic resulted, though in the next year plague prevailed in the adjacent parts of Mozambique. In 1898 or 1899 plague appeared at Port Louis in Mauritius, where it has continued ever since; it was thought to be derived from Tamatave. In 1899 Penang in the Straits of Malacca, and Manila in the Philippines, were affected. In the Pacific, Numea in New Caledonia, and Honolulu in the Sandwich Islands received the infection. In Australia, Sydney had a definite though limited epidemic, clearly traced to rats in the port, but whether from Hong Kong or from Numea was uncertain. There was a limited epidemic in Queensland, while Melbourne, Adelaide, Perth, and Auckland received some imported cases, but the epidemic was arrested. Western Europe, after nearly two centuries of exemption, witnessed a serious epidemic of plague at Oporto in 1899, or perhaps originating earlier. The source whence it was infected was not clear, but probably it came from India. Lisbon suffered later, but less severely. So strange are the ways of plague, that from Oporto the Western Hemisphere for the first time in history became infected. Plague was first recognised at Asuncion, an inland port on the river Plate, and it afterwards appeared at Santos in Brazil, Rosario on the river Plate, Buenos Ayres, and Rio de Janeiro. In the same year plague appeared in its old home, Egypt, at Alexandria, on the highway between India and Europe. It has more than once since reappeared in Egypt, but that it has not taken root in that classic land of plague must be set down to the excellent measures taken by the Egyptian medical authorities.

In North America, San Francisco has more than once been the scene of small epidemics of plague, confined to the Chinese quarter and apparently introduced from China. Some ports in Mexico are said to have been infected with plague, but the evidence was not quite complete. The disease has been carried to New York by shipping, but has not caused any epidemic.

In 1900 plague again crossed the Atlantic, this time from West to East, being brought by a ship from Rosario to Cape Town, where, in spite of quarantine precautions, it invaded the city and spread also to Port Elizabeth. Other outbreaks in South Africa were reported during the war and since, chiefly in the ports, but one outbreak occurred at Johannesburg. The plague, however, does not seem to have taken root seriously in that country.

Recently plague has spread to new regions. Towards the end of 1905 it broke out in Seistan, a district in the East of Persia, bordering on Afghanistan, quite remote from the older seats of plague in Western Persia, bordering on Kurdistan. It seems probable that this epidemic was derived indirectly from India, but the connexion cannot be precisely traced. A great mortality among rats was observed.

A fresh recurrence has been observed during the winter 1905-6 in the Russian province of Astrakhan, on the banks of the Volga, at Krasnoi Jar, close to Vetlanka, the scene of the fatal outbreak of 1879.

The mortality was not large, but the rate of case-fatality was 95 per cent. No mortality among rats has been recorded. Recent outbreaks in the neighbouring districts bordering on the Caspian make it probable, as some think, that there is an endemic centre of plague in those regions.

Plague has continued to prevail in its old seats, Hong Kong and Southern China, while epidemics are reported from Japan, Formosa, and Mauritius, but on the whole with diminished mortality. From the South American ports, as Rosario and Buenos Ayres, plague is still reported from time to time ; and on one occasion occurred on a steamer arriving from those parts at Hamburg, but did not spread to the port.

The small epidemic at Glasgow in 1900 was the first known in Britain since the great plague of London. It was strictly limited by preventive measures, but affected about thirty persons, of whom eight died. Contrary to the experience of almost all recent epidemics in seaports, no mortality among rats was observed, and the source of infection was not traced (*vide* p. 378). Since the general diffusion of plague by sea traffic, cases have been imported to several British ports—Liverpool, King's Lynn, Cardiff, Bristol—and a few have been brought to London, but it has always been found possible to prevent an epidemic. In May 1906 a few cases occurred at Leith, possibly due to infected rats.

In Australian and South African ports plague-infected rats have been on several occasions detected, but no human epidemic has resulted.

On the whole plague has shewn in all parts of the world diminished virulence and less tendency to spread.

J. F. P.

Bacteriology.—The cause of plague is the *Bacillus pestis.* During the Hong Kong outbreak in 1894 the Japanese Government sent Kitasato and Aoyama to investigate the disease. Arriving at Hong Kong on 12th June, Aoyama made an autopsy on 14th June, and Kitasato found numerous bacilli in the buboes, heart-blood, liver, and spleen. Similar bacilli were also found in a living case of plague on the same day. On 15th June cultures had developed, and with the exception of pigeons, all the animals inoculated by Kitasato died with signs identical with those of human bubonic plague. Yersin, sent by the French Government, arrived in Hong Kong on 15th June, and independently discovered the same bacillus, which has since been called *Bacillus pestis.* In the twelve years which have elapsed since the discovery of Kitasato and Yersin an immense literature on the plague bacillus has accumulated, and it has been identified all over the world as the cause of plague. In the great Indian outbreak it was studied by Hankin, Childe, Haffkine, and others, and as the epidemic increased in magnitude Commissions sent by various European Governments proceeded to India, working especially in Bombay. The results of their investigations have been published in a series of reports, of which the most important are the splendid work of Albrecht, Ghon, and Müller of the Austrian Commission (3), the report of the German Commission (19) (Gaffky, Pfeiffer, Sticker, and Dieudonné), the exhaustive analysis of the Indian Plague Commission (Fraser, Wright, and Ruffer), and the Reports on Plague Investigations in India issued by the Advisory Committee appointed by the Secretary of State for India (1906) [77A]. The Russian Commissioners (Wyssokowitch and Zabolotny) also contributed many valuable additions to our knowledge. Apart from India and Hong Kong, the bacillus was studied in Formosa (Ogata (73) and Yamagiwa), Alexandria (Gotschlich (31)), Japan (Kitasato and Shiga), Sydney (Thompson and Tidswell), Oporto (Kossel (56), Calmette (9), Vagedes), and in South America (Voges and Uriarte).

A number of laboratory studies have also been completed in Europe, mostly in special plague laboratories by Nuttall, Kolle, Otto, Martini, and Kossel in Berlin; by Markl in Vienna; by Roux and Metchnikoff in Paris; Lustig and Galeotti in Florence; Abel and Nocht in Hamburg; and by Klein, Hewlett, and Douglas in London.

Protection of human beings has also been carried out on a large scale in India, chiefly through the efforts of Haffkine with his plague vaccin.

At the present time we possess a fairly complete knowledge of the pure bacteriology of the plague bacillus. A great deal, however, still requires to be done, especially concerning the manner in which the bacillus is transmitted, and concerning the best means for producing a specific prophylaxis and cure.

Plague belongs to the group of Pasteurelloses (Lignières) or hæmorrhagic septicæmias (Hueppe), diseases due to microbes which are highly pathogenetic to vertebrates. In all cases these microbes invade the blood-stream acutely, and are found in large numbers over the whole body.

Morphology of the Plague Bacillus.—The plague bacillus as seen in plague lesions (bubo, blood) shews a considerable polymorphism. In general three forms may be readily recognised, viz., short oval rods, long rods, and large oval, pear-shaped or round pale-stained involution-forms. Of these the predominating form is the short oval rod measuring 1·5 to 1·7 $\mu \times$ ·5 to ·7 μ (Albrecht and Ghon). The involution-forms occur most frequently in artificial media and in cadavers which have been maintained at relatively high temperatures (30° C.). The onset of involution in cadavers has been studied by Sata, who finds that from the second day after death the bacilli begin to alter, especially in the liver and spleen. The alteration proceeds up to the fourth day, but after this time the plague bacillus could not be identified with certainty, as it was overgrown by other microbes. The tendency to the formation of involution-forms is important from a diagnostic point. In pure cultures all the forms of plague bacilli mentioned above are also met with. The occurrence of club-like swellings and branches on plague bacilli has been described by Albrecht and Ghon, Kolle (52), and Sksehivan (87).

Staining.—The plague bacillus exhibits in a high degree the phenomenon of polar staining, the micro-organism appearing stained at the ends but not at all or only slightly so in the middle. This can be well seen in

films stained by Romanowsky's method, or by first treating the film with dilute acetic acid followed by dilute carbol-fuchsin. Kossel and Overbeck recommend fixing the films in absolute alcohol which is then evaporated off. Although a striking feature of the plague bacillus, polar staining is by no means peculiar to it, as other Pasteurellæ closely allied to the plague bacillus may shew the same phenomenon. It is often difficult to stain the plague bacillus well in sections. Sublimate or alcohol are the best fixatives for plague tissues, the most suitable stains being carbol-thionin, or polychrome methylene blue with glycerin-ether treatment. The Unna-Pappenheim methylgreen-pyronin mixture gives very instructive pictures, the bacilli standing out of a brilliant pink colour. Although Kitasato described the plague bacillus as retaining to a certain extent the stain in Gram's process, other observers have all found it to be Gram negative. Contrary to the opinion of Kitasato and Gordon the plague bacillus is non-motile. Endospores have not been observed, and from the experiments made on the resistance of the bacillus to injurious influences, it is improbable that they are formed. In their earliest descriptions both Kitasato and Yersin described the occurrence of a capsule surrounding the plague bacillus. It can easily be seen in cultures and even in bubonic pus by Romanowsky's method or any of its modifications.

Cultures.—Growths of plague bacilli can be obtained between wide ranges of temperatures, viz. 4° to 43° C. Unlike most pathogenetic bacteria the optimum temperature for growth is about 30° C., a higher temperature being very apt to produce attenuation in the virulence. Although it can grow to a certain extent under anaerobic conditions, aerobic are much more favourable. On the surface of an *agar* plate at 30° C. colonies of plague bacilli are visible under a low magnification as small drops, like dew, at the end of twenty-four hours. In forty-eight hours they have a whitish-grey colour with transmitted light. The centre is usually granular and in characteristic colonies there is a broad irregular or crenated edge. It has been repeatedly noted that atypical colonies of a yellowish-grey colour and with a regular edge make their appearance. The times at which the colonies appear on the plate are also different, some being delayed as late as forty-eight hours. Streaked on agar a fine greyish-white mass of somewhat slimy consistence develops in twenty-four to forty-eight hours.

Salt Agar.—On adding 2·5 to 3·5 per cent of sodium chloride to ordinary agar, Hankin and Leumann found that there was a very rapid development of involution-forms, the staining properties of which are usually very poor. The value of these forms, from a diagnostic standpoint, is considerable, as they occur quicker, and with greater certainty in the case of *Bacillus pestis* than in the case of other bacteria which may otherwise closely resemble the plague bacillus. (Skschivan (87), Rosenfeld, Matzuschita.)

On the surface of *gelatin* plates, cultivated at 20° to 25° C., colonies of *Bacillus pestis* become visible to the naked eye in two to three days. At first transparent, they soon become greyish with a raised granular centre and a filmy crenated flat margin. The structure of such colonies can be very clearly made out in contact preparations. As in the case of agar, the individual colonies differ from each other in their rate of growth, and also to a certain extent in appearance. Thus, Dr. Klein (48) has described atypical colonies which were not unlike growths of *B. coli*, and were composed of the short oval rod form of the bacillus, whereas in the "typical" colonies the bacilli are usually larger. In a gelatin stab-culture a thread-like growth appears in the track of the needle with a surface growth similar to that seen on a gelatin plate. The gelatin is never liquefied.

The growth on peptone *bouillon* has been described as characteristic. At first, a general cloudiness makes its appearance, then a deposit. Round the edge of the vessel a whitish ring of growth ensues, and this finally spreads over the surface as a fine membrane. As Haffkine shewed, a layer of oil or ghee favours the surface growth, the bacilli hanging down from the oil-drops in the form of stalactites. This stalactite formation is not, however, peculiar to *Bacillus pestis.* In old bouillon cultures the medium appears clear above and shews a granular deposit below. After three to four days the growth in bouillon often seems to stop, to reappear again and to go on for weeks. Indol is not produced.

In general the cultural diagnosis of the plague bacillus rests on the appearance of the surface colonies on gelatin at 20° to 25° C., and on agar at 30° C., the former being especially useful when the plague material is contaminated with other bacteria as occurs in fæces, sputum, etc.

Vitality of the Plague Bacillus outside the Body.—A very large number of experiments have been made to determine the degree of resistance which the plague bacillus manifests outside the living body. In general the resistance is slight. Pure cultures kept in the dark and prevented from drying can live for months or even years (N. K. Schultz (84)); a great deal depends, however, on the temperature at which the experiments have been carried out. Thus when kept at 37° C., Gladin found cultures alive up to two to three months, whereas at 15° C. living bacilli were still found for 260 days. Difference of opinion prevails as to how long the bacillus can exist in the presence of other bacteria. The German Plague Commission saw plague bacilli growing freely in cultures along with *B. coli*, whereas the Indian Plague Commission found in such experiments that the plague bacillus quickly died out. The German Plague Commission recovered living plague bacilli from a spleen which had been putrid for four days. From the putrid cadavers of plague rats, Otto (76) was able to demonstrate the plague bacillus (by inoculating guinea-pigs) up to sixty-one days provided that the cadavers had been kept at a low temperature (6° C.). In bubonic pus Albrecht and Ghon found that the bacillus could survive for twenty days. With sterilised fæces inoculated with plague bacilli, growths were obtained up to the fourth day (German Plague Commission). In fresh water the bacillus has been found to exist as long as twenty days (Wilm, Abel (1)). Wurtz and

FIRST PROOF

Bourges recovered plague bacilli in a virulent condition from sea-water after forty-seven days.

In previously sterile earth, in which the organic matter had been destroyed by heat, Gladin found the bacillus for two weeks, whereas if the organic matter were present it could live for three months. Even in non-sterilised earth Gladin was occasionally successful in getting cultures as late as two months. Marsh found that the plague bacillus could live for months in sterile cow-dung. The Advisory Committee on Plague in India (1906) made a number of experiments on the infectivity of floors grossly contaminated with cultures of *B. pestis.* Throughout India there are two common forms of floors, the one consisting of ordinary cow-dung plastered, when moist, on the top of beaten earth, the other consisting of a mixture of lime and sand, and commonly called "chunam." On cow-dung floors it was found that plague bacilli remain infective for forty-eight hours, as tested by inoculating scrapings into rodents. If the latter are permitted to run free on such floors infection was not observed later than twenty-four hours. In the case of grossly infected floors of "chunam" the destruction of the plague bacillus took place within twenty-four hours.

In buried bodies plague bacilli have been recovered at periods varying from three (Gottschlich) to thirty (Yokote) days. Sata and Klein (47A) were able to recover the bacilli from the bodies of guinea-pigs that had been buried for sixteen and seventeen days respectively. Zlatagoroff (113) found, however, that if cadavers were kept at 0° C., living plague bacilli could be grown even after 109 days.

Resistance to Drying.—Bubonic pus dried on a cover-glass at 28° to 30° C. was sterile after four days (Kitasato). In numerous experiments carried out by the German Plague Commission, plague material being dried on wool, silk, linen, glass, wood, etc., the latest period at which the plague bacillus was found alive was six days. Drying in an exsiccator over sulphuric acid at 29° to 31° C. is rapidly fatal to plague bacilli (Wilm, Abel (1), de Giaxa and Gosio, Gladin), but much depends on the temperature at which the experiments are carried out. In dust the bacillus appears to die out rapidly, Germanno finding that bacilli dried to a fine dust had been killed. This suggests that transference of plague by currents of air, except at very short ranges, is improbable. In grain and meal the plague bacillus died out within thirteen days (Hankin).

Exposure to light causes rapid sterilisation of plague cultures or other infected material. From bubonic pus dried on cover-glasses and exposed to light, Kitasato was unable to obtain living cultures after three to four hours.

Heat.—Dry heat at 100° C. kills plague bacilli in one hour (Abel (1)) at 140° C. in three minutes, and at 160° C. in one minute (Gladin). Experiments which have been made on the action of moist heat have yielded somewhat divergent results, no doubt because the individual bacilli possess varying degrees of resistance. At temperatures of 55° to 70° C. the German Plague Commission obtained sterilisation of cultures in ten minutes.

Albrecht and Ghon and Gottschlich found that even after being heated to 55° to 60° C. for one hour cultures might still be infective for animals, although the media inoculated from such cultures remained sterile. Gottschlich heated agar emulsions to 68° C. for twenty minutes, and then kept them at 65° C. for sixty minutes, and found that although they were apparently sterile, they were still infective. Kolle, however, maintains that if the culture mass be frequently shaken during the process of heating, a temperature of 65° C. renders it both sterile and non-infective. Dr. Klein (47) also regards a temperature of 65° C. as effective.

Exposure to *cold* has very little effect on the plague bacillus, as it can survive at a temperature varying from 0° C. to – 20° C. for as long as forty days (Wladimiroff and Kressling). Kasansky even found it alive in 5½ months at a temperature of – 31° C.; Gladin froze and thawed cultures daily, and the bacillus was still alive after forty days of such treatment.

Resistance to Chemical Disinfectants.—Cultures of the plague bacillus are easily destroyed by chemical antiseptics; thus perchloride of mercury (1 per cent) destroys the vitality at once, 1 per cent carbolic acid or 1 per cent lysol in ten minutes, 1 per cent chloride of lime in five minutes, sulphuric acid 1 in 2000 also in a few minutes. No extensive series of experiments have been carried out on the chemical disinfection of plague bacilli under natural conditions in houses, soil, clothes, etc.

Pathogenetic Action.—The plague bacillus exerts a pathogenetic action on a large number of animals. Prominent among these in point of susceptibility are rats, guinea-pigs, mice, and monkeys, which succumb with septicæmia in a few days after the inoculation of very minute quantities of plague material. In other cases as in the horse, dog, cat, sheep, cattle, goats, and pigs, inoculation is followed by a rise of temperature and the formation of a local lesion, ending mostly in recovery. Unless inoculated with enormous doses of highly virulent cultures, all birds shew a very high degree of immunity. In discussing the pathogenetic effects in animals, most stress must be laid on plague in rats, as there is a close connexion between plague in these rodents and outbreaks in man.

Experimental Plague in Rats.—All varieties of rats can be infected with the greatest ease through almost any channel. After subcutaneous inoculation of a minute quantity of a virulent plague culture the animals manifest definite symptoms of illness within thirty-six hours; the hair is ruffled, the breathing rapid, and a peculiar nervousness or apprehension is usually a striking symptom. The temperature is raised and the conjunctivæ suffused. At the site of the inoculation there is usually a definite swelling which increases up to the time of death, which in acute cases supervenes about the third day. The characteristic lesions seen after death are the enlargement of the regional lymph-glands which are deep red, while the surrounding connective tissue is œdematous and frequently hæmorrhagic. The spleen is much enlarged, dark and firm, and generally presents a peculiar dry surface on section. The lungs are more or less

congested and occasionally shew petechiæ. Enlargement of the mesenteric glands is constant and the intestine is hyperæmic. In the blood-stained mucus found in its lumen plague bacilli can be demonstrated as in all other parts of the body. They are, however, in greatest numbers in the spleen and buboes. In some cases death may be delayed till the fifth to seventh day in which cases necrosis of the buboes has set in. When the cultures are very toxigenic the post-mortem appearances of plague may be masked and the bacilli not so uniformly distributed.

Cutaneous Inoculation.—Peculiar interest attaches to the effect of applying plague cultures superficially to shaved areas of skin. The value of this method was first noted by Albrecht and Ghon in the case of guinea-pigs. Kolle had only partial success, however, in the case of rats. In Captain Douglas's hands this was found to be a very effective method of producing a fatal pest septicæmia, for out of 167 experiments on rats only 3 per cent survived. Technically this method of inoculation is best carried out by placing the rat in a holder and shaving a strip in the middle line between the teats. A glass rod dipped in an emulsion of plague bacilli is then applied to the shaved area over an extent of one square centimetre. At the time of death, which usually occurs on the second to fourth day, the local lesion in the shaved area consists of three to six small vesicles with a slightly raised and inflamed base. The fluid of the vesicles contains an enormous number of plague bacilli and a few degenerated leucocytes. Where the skin has been less carefully shaved the whole area over which the culture was spread may be thickened, reddened, and rough, but without vesicular formation. Buboes are present in all cases, even when the animal succumbs as early as the second day. The buboes, mostly axillary in position, vary in size but are always teeming with plague bacilli. Suppuration of the buboes may occur in cases that recover or do not die till the seventh to tenth day. When a culture of plague bacilli has been applied to the skin of immunised rats the local lesion may be entirely absent; at other times a large ulcer involving the whole thickness of the skin results. Occasionally the local change is in the form of a carbuncle-like swelling in which the skin is undermined by pus which escapes through a number of openings. Intraperitoneal inoculation of very minute quantities of cultures produces a rapidly fatal septicæmia. In some cases death seems to take place mainly from intoxication, the bacilli being found chiefly in the peritoneum over the liver and spleen.

Infection by the Mouth.—When rats are fed on plague cultures or on plague cadavers, the bacilli become localised in the submaxillary lymphatic glands and give rise to buboes in this site. Later, the animals fall victims to a plague sepsis. Kolle saw submaxillary buboes in forty out of sixty rats infected *per os.* In four other cases the result was a primary pest pneumonia, and in two cases only the development of mesenteric buboes shewed that the bacilli had passed through the intestinal wall. Captain Douglas was not so successful in experiments of this kind. Under natural conditions rats frequently infect themselves by gnawing the pest cadavers of other rats, the bacilli gaining entrance through small abrasions in the nose and mouth and leading to buboes about the jaws.

In the intestine necrotic changes may be found in Peyer's patches. In half of Kolle's cases bacilli were also found in large numbers in the blood and organs. The fæces of rats infected by the mouth may contain virulent plague bacilli (German Plague Commission).

The German Commission were the first to shew that the inoculation of plague cultures on the unbroken nasal or conjunctival mucous membrane leads almost invariably to a fatal issue, in about three days, with cervical bubo and enlargement of the spleen. Batzaroff stated that a primary pest pneumonia frequently ensues after cultures have been inserted into the nose, but Bandi proved that in such cases the pneumonia is really secondary to the cervical bubo. The development of buboes in the neck after conjunctival inoculation is probably the result of the bacilli passing down the nasal duct into the lymphatic apparatus of the throat.

Plague Pneumonia in Rats.—Martini produced primary pest pneumonia in rats in thirty-two out of thirty-six experiments by causing them to inhale plague cultures atomised into a spray. The lesions in the lungs were sometimes lobular, sometimes lobar; pleurisy was frequent. Martini thought that the virulence of the cultures was exalted by passage from lung to lung, and that when these exalted bacilli were inoculated intraperitoneally or subcutaneously they had a great tendency to become localised in the lung.

Chronic Rat Plague.—Kolle and Martini have drawn attention to the occurrence of a chronic form of rat plague manifesting itself in encapsuled foci with caseous contents in the submaxillary and bronchial glands, and associated with induration of the lungs. Chronic rat plague has also been investigated by Captain Douglas, who found the bacilli localised in lesions of the lungs, spleen, and glands. In 104 partially immunised rats dying before the eleventh day after inoculation with virulent plague material, a lesion was found in the lungs and usually associated with pleurisy. In a few cases dying late (eighth to tenth day) or surviving after the eleventh day, Douglas found numerous sharply circumscribed small nodules of whitish colour in the spleen. The nodules, which often numbered several hundreds, were exactly like the lesions of chronic plague or pseudo-tuberculosis seen in guinea-pigs. The spleen for the most part was much enlarged by the presence of the nodules, which contained large numbers of plague bacilli, especially in the centre. Chronic plague lesions were also met with in the liver and thymus glands, although the animals were apparently in good health. In chronic pulmonary or splenic plague emaciation is a common symptom. In two cases in which the bacilli, isolated from chronic lesions, were tested, they were found to be attenuated. In Kolle's experiments, however, it is to be noted that the bacilli were virulent.

Experimental Plague in Guinea-pigs.—Like the rat, the guinea-pig exhibits an extreme susceptibility to the plague bacillus, fatal infection

ensuing after cutaneous, subcutaneous, intraperitoneal, intranasal, and conjunctival inoculation, or from inhalation, or ingestion of plague cultures. The symptoms and signs of experimental plague in guinea-pigs are identical with those described in the case of the rat. Chronic plague in the guinea-pig, with the production of large granulomatous masses in the liver, peritoneum, and spleen was first noted by Albrecht and Ghon.

Mice appear to be less susceptible to plague than either rats or guinea-pigs, although virulent cultures usually induce a fatal septicæmia in three to five days. Infection *per os* often yields negative results.

Unless virulent cultures are employed, rabbits often escape on account of a considerable degree of insusceptibility which they possess. Mungooses (*Herpestes*), squirrels (*Sciurus*) (German Plague Commission), bats (*Vesperugo* (Gosio)), jerboas, and sisels (Tartakowsky), are highly susceptible to plague. Sksehivan inoculated a tarbagan (*Arctomys bobac*) subcutaneously, and produced a general pest sepsis with hæmorrhagic pneumonia, without local lesion or bubo. As was first shewn by Wyssokowitch and Zabolotny in Bombay, monkeys are highly susceptible to plague virus, a prick in the finger with a needle dipped in a culture leading to pest sepsis and death. Similar results were obtained by Albrecht and Ghon and by the German Commission. *Semnopithecus entellus* was found to be much more susceptible than the brown monkey of India (*Macacus radiatus*). Captain Douglas produced fatal sepsis in monkeys from conjunctival, nasal, and vaginal inoculation of minute quantities of plague cultures. Intratracheal inoculation gave rise to primary plague pneumonia. After ligation of the femoral or brachial veins, injection of plague cultures into the corresponding limbs caused typical buboes, sepsis, and death in a few days.

Dogs, jackals, and hyænas are mostly insusceptible, even after subcutaneous inoculation (Albrecht and Ghon). Plague bacilli may be passed per rectum after ingestion of plague-infected material. Ogata was able to infect cats, but the details of his experiments are not known. In the hands of the German Commission subcutaneous inoculation of cultures caused fever and local reaction, ending ultimately in recovery. Wilm, Kolle, and Hunter saw cervical buboes in cats fed on plague material. In four animals treated in this way Kolle had two positive results, one dying from pest sepsis with cervical bubo, the other recovered after a severe illness with great emaciation.

Pigs.—Wilm in Hong Kong observed a rise of temperature and local œdema after subcutaneous inoculation in the flank. Dr. Lowson fed swine with large quantities of plague spleens, but they recovered. The German and Austrian Commissions, and also di Mattei, had similar negative results.

Horses usually react with local lesion and fever (Yersin, Calmette, and Borrel), and the same applies to cattle, sheep, and goats. Hedgehogs are immune (Nuttall), as are pigeons, fowls, ducks, singing-birds (Albrecht and Ghon, London), lizards, serpents, salamanders, and frogs (Nuttall). Devell states that he had positive results with *Rana temporaria*.

Behaviour of Plague Bacilli in the Bodies of Insects.—A very extensive literature exists on the part played by insects in the dissemination of plague; the animals specially studied in this connexion being flies, bugs, mosquitoes, pediculi, ants, cockroaches, and fleas. Considerable differences might be expected according as the insects are suctorial or not, or according as those which infest animals such as rats, are capable of transferring themselves to the body of man. In non-suctorial insects the plague bacillus may exist on the surface of the body, and may in this way be transferred to articles of diet, clothing, and so forth. Extreme interest also attaches to the question of the fate of the plague bacillus in the alimentary canal of the insects, and especially whether it is capable of multiplying in this site or undergoing changes in virulence either in the direction of exaltation or attenuation.

Flies.—In at least one instance Yersin found plague bacilli in the bodies of dead flies in the laboratory at Hong Kong, Dr. Nuttall also succeeding in infecting *Musca domestica*, and he considered that flies might act as disseminators of the disease. Dr. Hunter examined flies caught in the plague wards and in the public mortuary in Hong Kong during a plague epidemic; washings obtained from the bodies of the insects did not shew plague bacilli, whereas emulsions made from crushed-up flies shewed that 20 to 75 per cent were plague infected. He also found that plague flies were capable of infecting pieces of sugar over which they had been allowed to crawl. According to Dr. Hunter's evidence, plague bacilli may remain virulent in the intestine of the fly for forty-eight hours. In Manila, Herzog had negative results with cultures made from flies.

Bugs.—Experimentally, Dr. Nuttall found that plague bacilli can be recovered from the intestine of ordinary bed-bugs up to seventy-two hours after they had sucked the blood of rats suffering from plague, but it was impossible to transmit plague through the agency of these insects.

According to the testimony of the Austrian and German Commissions, it is unlikely that the transmission of plague takes place by the *Mosquito.* Dr. Hunter also failed to find bacilli in the body of mosquitoes even when they had been caught under the mosquito nets of plague patients. In the Arthur Road Hospital in Bombay no transfer of plague from the sick to the healthy took place although the staff and attendants were constantly bitten by mosquitoes (Choksy (41)). Cultures made from *pediculi* obtained on the bodies of plague patients were negative in Dr. Hunter's hands. It was suggested by the Indian Commission that the unusually high incidence of plague among the Jains in India might be referable to transmission by pediculi. This race, as is well known, has an aversion to taking any life, and are, in consequence, infested with lice. In Manila, Herzog found plague bacilli in three lice (*P. capitis*) from a child dead of plague.

Ants.—Dr. Hankin believes that certain *ants* (*Monomorium vastator*) can transmit plague, and they often succumb after feeding on plague rats.

Cockroaches.—Dr. Hunter maintains that this insect (*Blatta orientalis*)

may harbour plague bacilli and carry them for a considerable distance. He was able to recover cultures from the fæces of cockroaches.

Fleas.—Since Ogata was able to infect mice by means of fleas, which had sucked the blood of pest-infected rats, these insects have been the subject of much study. Simond especially developed the flea hypothesis of the transmission of plague, by trying to establish that plague rats are eminently infective when infested with fleas. He considered that when deserted by their parasites, rats cease to be dangerous, and that plague can pass from infected rats to other animals which have not been directly in contact with them or with their infected excretions. Loir went so far as to affirm that the fleas of rats are the main agents through which the disease is transmitted to man. Kolle and Nuttall obtained negative results in attempting to infect healthy rats with fleas obtained from plague-stricken animals. The Indian Plague Commission, from analysis of the data on the subject of fleas and plague, came to the conclusion "that Simond's proposition that suctorial insects play an important part in the transmission of plague from sick to healthy animals is so weak as to be hardly deserving of consideration." In recent years attention has been directed mainly to the question, whether rat-fleas are capable of biting man. According to Galli-Valerio (20) the common fleas (*Typhlopsylla musculi* and *Pulex fasciatus*) of the European rat do not attack man, and Tiraboschi is of a similar opinion. In 100 rat-fleas examined by Tidswell in Australia the incidence of the different varieties worked out as follows: *Pulex fasciatus*, 10 per cent; *Typhlopsylla musculi*, 8 per cent; *Pulex serraticeps*, 1 per cent; and *Pulex pallidus* (*P. cheopis* Rothschild), 81 per cent. Of these the last, according to Tidswell, Gauthier and Rayband, and Tiraboschi (94), can attack man. On ship-rats Tiraboschi found that 40 per cent of the fleas belonged to *Pulex murinus*. Both *P. murinus* and *P. pallidus* have been subsequently identified as *P. cheopis* Rothschild. In five experiments, Gauthier and Rayband succeeded in conveying plague from rat to rat by fleas, and they also identified *P. pallidus* as present upon ship-rats. Zirolia states that even *P. irritans* and *P. serraticeps* can retain plague bacilli in their bodies for seven to eight days. Captain Liston made the important observation that whereas in Europe *Pulex* (*Ceratophylus*) *fasciatus* and *Typhlopsylla musculi* are the common rat-fleas, their place to the extent of 99 per cent is taken in the case of the Indian rat by a non-pectinated flea—*Pulex cheopis* Rothschild. Mainly through the researches of Major Lamb and Captain Liston, remarkable advances have been made in our knowledge of the flea-plague question during 1906. They have shewn that the common Indian rat-flea (*P. cheopis*) can transmit plague from an infected to a healthy rat confined in close proximity, but protected in such a way as to prevent direct infection. In 55 per cent of the experiments healthy rats living in flea-proof cages contracted plague after receiving fleas collected from rats dying of septicæmic plague in other cages. Experiments were also made in a series of cabins—so-called "go-downs"—constructed to imitate the conditions obtaining in the spread of plague in man, guinea pigs and monkeys being used. The essential differences in the construction of the various experimental "go-downs" were in the roofs, and especially whether the latter permitted rats to harbour in them, and whether light was permitted to enter or not. It was found that if fleas were excluded, the closest contact of plague-infected animals with healthy animals did not give rise to an epizootic among the latter. If fleas were present, an epizootic once started spread from animal to animal, the rate of progress depending directly on the number of fleas present. It is possible even for an epizootic of plague to start without any direct contact of healthy and infected animals. Infection may also take place without actual contact with contaminated soil, and that this is not due to aerial infection is shewn by the observation that animals, suspended a suitable distance above a soil grossly contaminated with plague-material and above plague-stricken animals infested with fleas, escape the disease. In plague-infected human dwellings, guinea-pigs can contract plague by becoming infested with plague-infected fleas, and this even in houses which have been disinfected. In some experiments animals, protected and unprotected against fleas, were exposed side by side in plague-infected houses with the result that the former remained free from the disease, while a number of the latter succumbed to plague. The dissection of seventy-seven fleas caught in infected houses shewed that twenty-three harboured *B. pestis*. These experiments, which have been published in the reports on plague investigations in India, issued by the Advisory Committee appointed by the Secretary of State (1906), seem definitely to prove that under natural conditions the rat-flea is an important agent in the dissemination of plague. In the case of non-suctorial insects the dissemination of the bacillus may also be brought about indirectly.

Spontaneous Plague in Animals.—The plague bacillus frequently infects animals in natural conditions, the different groups attacked being widely separated from each other in the zoological scale.

Primates.—Epidemics of plague in monkeys occurred in the modern Indian epidemic in several places, especially at Hubli, Ankleschwar, Dharwar, and Kankhal. In Hardwar and the neighbourhood, Dr. Hankin isolated plague bacilli nine times in twenty-six cases. Both the highly susceptible langurs (*Semnopithecus entellus*) and the brown monkey (*Macacus radiatus*) succumbed to plague in the above places.

Carnivora.—Dogs and cats, especially the latter, occasionally develop plague. In India this was noted in Bombay, Karachi, Bandra, and in particular at Ahmednagar, which was overrun with cats having open buboes in their necks. Ashburton Thompson saw spontaneous plague in cats in Sydney; Dr. Hunter the same in Hong Kong. In the South African epidemics at Port Elizabeth, East London, and King William's Town, numbers of cats were proved to be suffering from plague (Mitchell).

Ungulata.—Cattle, sheep, goats, and horses are not known to contract plague spontaneously. Some have reported epizootics in pigs during

plague epidemics, but it is very doubtful whether the animals succumbed to the genuine plague bacillus, or to other forms of hæmorrhagic septicæmia.

Rodentia.—Bubonic plague has frequently been seen to affect rodents. Thus, a great plague mortality occurred among squirrels (*Sciurus palmarum*) in the Indian epidemic, especially at Hubli, Bangalore, Poona, and other places. Of special interest is a disease—in all probability true plague—which periodically decimates the Siberian marmot or tarbagan (*Arctomys bobac*) in Transbaikalia and Mongolia. This tarbagan plague was first reported by Beliarsky and Reschetnikoff at Akscha on the Chinese frontier, the marmots shewing buboes in the axillæ and groins. It is believed that the tarbagan pest is highly contagious to man, and it was proved beyond doubt by Zabolotny that genuine bubonic plague is common in Eastern Mongolia. Rudenko also considers that tarbagan plague and human plague are identical, the susceptibility of the tarbagan to cultures of *Bacillus pestis* has been referred to on p. .

Spontaneous Plague in Rats.—By far the most important animals in this connexion are rats, the occurrence of spontaneous plague in which is one of the constantly observed features of the modern plague pandemic. As Abel (2) has shewn, the older literature, with the exception of notices by Avicenna and Orraeus, is practically devoid of references to spontaneous disease in rats preceding or accompanying bubonic plague in man.[1] Marked attention was directed to rats in 1894, when large numbers succumbed to plague in Canton and Hong Kong (Yersin). The incidence of rat plague in India has been fully analysed by the Indian Plague Commission, the most striking outbreaks occurring at Mahlghala, Chak-Khalal, and Banga. According to Kitasato rats were infected to the extent of 10 per cent in Osaka, and 20 per cent in Kobe (Japan). Plague in rats was also seen in Formosa, Mongolia, and in the Philippines. In Africa vast plague mortality in rats occurred in Kisiba (Koch and Zupitza); to a less extent the same was seen in Alexandria (Gottschlich), Lorenço Marquez (Vaz), Port Elizabeth (Blackmore), Durban, and Maritzburg (Hill), Réunion (Maxse). In Australia human plague in Sydney was constantly preceded by rat plague (Thompson and Tidswell); in Europe plague epizootics in rats occurred in Oporto (Kossel and Frosch), in Naples (Santoliquido), and in the Odessa epidemic of 1901-2 (Rabinowitsch and Kempner, Skschivan). In South America a similar state of affairs prevailed in Asuncion and in Rosario (Uriarte), likewise in Brazil (Havelburg) and in Peru. In several parts of India, however, no connexion could be traced between rat and human plague. The same applies to the Kolobowka epidemic (Tartakowsky). In the Glasgow epidemic in 1900 no plague could be found in the rats, nor was there any evidence that rats played a part in the dissemination of the disease. In 1901 and 1902, however, large numbers of plague-infected rats were found, and in several instances in houses in which human beings had contracted the disease in 1901. The species of rats which have been found to suffer from plague are *Mus decumanus* (brown rat), *Mus rattus* (black rat), and its variety *Mus alexandrinus.* There does not appear to be any difference in susceptibility among the various species of rats. Autopsies on plague rats shew the same changes as those met with in the experimentally produced disease. Of peculiar interest is the occurrence of *chronic* forms of spontaneous plague, which may possibly be the means of bridging successive epizootics (*vide* p.) (Hunter).

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[1] In modern times the death of rats during or before epidemics of human plague was first noticed in India, viz.: in Kumaon, 1834-35, by Gowan; in the Pali plague, 1836-38, by Forbes and White, and in Kumaon, 1853, by Francis and Planck. But there are records of rat-disease associated with human plague at least as early as the beginning of the seventeenth century in India, shewing that the phenomena were so striking as to arrest the attention of laymen as well as of physicians. Even in the ancient Hindu sacred book called *Bhâgavat Purana* (? ninth century, A.D.), mortality among rats is referred to as a sign of a coming plague. There is an equally definite account of rat-plague in Yunnan at the beginning of the nineteenth century, and probably it was observed there much earlier. It is thought that the reference in the first book of Samuel (vi. 5) to "mice that marred the land" during the plague of "emerods," which afflicted the Philistines, is an indication of plague among mice or rats; though biblical commentators give a different explanation.—J. F. P.

Occurrence in Rats of Diseases resembling Plague.—Since the modern outburst of plague spontaneous infections in rats have been frequently shewn to be due to bacilli other than *Bacillus pestis,* although the clinical and anatomical features led to the belief that the disease was genuine bubonic plague. Cases of this kind have been recorded by Danysz, Schilling, Aujezky, Kossel and Overbeck, Toyama, Neumann, Klein, and others. In most cases the bacilli found have been Gram negative and have shewn polar staining. The closest resemblance to *B. pestis* is shewn by Klein's *Bacterium bristolense,* which differs, however, in that abundant gas is developed in growths upon potatoes. Dr. Klein found it to be virulent for rats and guinea-pigs, except when applied cutaneously. *Bacillus pseudotuberculosis rodentium* (A. Pfeiffer) presents an extremely close resemblance to the plague bacillus (Galli-Valerio, Zlatogoroff, MacConkey), and can only be distinguished with the greatest difficulty. Mice are of much less importance than rats in connexion with the dissemination of plague; epizootics have, however, been observed among these rodents at Tai-ho-Kou (Formosa), at Jeddah, Alexandria, in South Africa, and in India at Bangalore, Porbandar, and other places.

Spontaneous plague has also been noted in the great bandicoot rat (*Nesocia bandicota*), in porcupines at Mysore, and in guinea-pigs at Sydney and Bangalore. At Knysna (S. Africa) veld rats (*Arvicanthus pumilio*) succumbed to plague in large numbers (Mitchell).

Marsupialia.—As a curiosity may also be mentioned the outbreak in the Zoological Garden in Sydney of spontaneous plague in wallabies and wallaroos (Ashburton-Thompson).

Variations in the Virulence of Bacillus Pestis.—Considerable variations occur in the virulence of the plague virus on artificial media, some strains becoming rapidly attenuated, while others remain highly virulent for years. Thus, Albrecht and Ghon isolated from a rat a strain of plague bacillus which, at the end of thirteen months was so virulent that $\frac{1}{100000}$ of a loopful killed a guinea-pig with acute

pest septicæmia. The best method for preventing a spontaneous attenuation of virulence is to keep the cultures in sealed tubes and at a low temperature. Cultivation at the body-temperature sooner or later leads to loss of virulence, a profound attenuation occurring if the bacillus be cultivated for long at 41° C. (Kolle). A convenient scale of virulence has been adopted by Kolle and Martini, the inoculations being carried out cutaneously in the guinea-pig with ·2 of a loopful of culture suspended in ·2 c.c. of bouillon.

a. non-virulent cultures—glandular swelling only ; slight emaciation.
b. weak „ —death in 2-3 weeks, with chronic pest granulomas in viscera.
c. medium „ —death in 8-10 days ; miliary nodules in spleen.
d. highly virulent cultures—death in 4-5 days ; septicæmia ; no nodular formation.

Exaltation of Virulence and Maintenance of Exalted State of Bacillus Pestis.—The plague bacillus can be exalted in virulence by passage through the bodies of guinea-pigs. The effect of its continued passage through rats is the subject of diverse opinion, Yersin, Calmette, and Borrel considering that rat passage produced attenuation. Drs. Hankin and Walton (41), were unable to continue the passages through rats. Even with intermediary subcultures between the passages, Captain Douglas observed great attenuation in the body of the rat. Otto (75), found that after twenty rat passages the bacillus no longer produced septicæmia, but only an intoxication, the bacilli becoming localised in the lymphatic glands without, however, being attenuated. The Advisory Plague Committee (1906) was able to infect twenty-six series of rats without recourse to artificial media, and was unable to find any alteration in virulence. It was found that Bombay rats vary considerably in susceptibility, and that a considerable percentage of rats in India are immune to the cutaneous method of inoculation. Passage through a series of rabbits appears to attenuate the bacillus for the rat (Otto).

Plague Toxin.—Experimentally a great deal of doubt exists in regard to the nature of plague toxin, and especially whether it is intra- or extra-cellular. Yersin, Calmette, and Borrel, Pfeiffer, Dieudonné, Dean, and the Austrian Commissioners, on finding that young plague culture filtrates are toxic only in large doses, concluded that the poison was an endotoxin. Markl, on the other hand, maintains that when grown at low temperatures the plague bacillus produces an extremely unstable exotoxin within twenty-four hours. As a result of his recent work, Kolle (54) agrees with those who regard the poison of the plague bacillus as mainly if not exclusively intracellular. With filtrates from young cultures he was unable to produce intoxication, notwithstanding the injection of relatively large quantities (3 c.c. in rats). On injecting the dead bacterial bodies, on the other hand, a rapidly fatal disease was produced, with profound symptoms of intoxication, referable to the nervous and cardiac tissues. If the animals survived the acute stage they succumbed later with marasmus, referable to parenchymatous degeneration of the heart, liver, and spleen. In general the filtrates increase in toxicity the older the culture, a maximum toxicity being obtained in cultures grown at 37° C. for three to four weeks. A peculiarity of filtrates from old cultures is that toxic symptoms come on at once and may cause death in one to two hours, a result due in all probability to secondary poisons, which have nothing to do with the primary pest toxin, the symptoms from which always make their appearance after an incubation-period, lasting six to eight hours. Pest serum has no effect in neutralising the secondary toxins. Besredka is of much the same opinion as Kolle. The toxicity of plague cultures grown on one and the same medium is very variable in its effects on rats, ·1 c.c. being occasionally fatal, while at other times 3 c.c. may produce only transient symptoms (Douglas).

Sites of Entrance of the Plague Bacillus into the Human Body.—In considering the portals through which plague bacilli pass into the body of man the skin is of primary importance. The deadly effect of applying a living plague culture to a carefully shaved area of the skin of rodents, proves that the bacillus can invade the body through minute breaches in the continuity of its surface. In all probability the same applies to man, although in the great majority of cases no definite primary lesion can be detected, and the bacilli first manifest their presence in the regional lymph-glands. That the bacillus can pass through the skin is shewn by the fact that the disease has in many cases been contracted by direct inoculation in the course of autopsies on plague patients. The Indian Plague Commission collected thirteen cases of this kind, and in only two of these (viz. Professor Sticker and Captain Leumann) was there a history of a primary vesicle or phyctenule at the point of inoculation. To these two cases must be added that of Professor Aoyama. Apart from post-mortem wounds the German Commission reported eleven cases in which primary plague vesicles were noted. Simond reported sixty-one such cases, and the Indian Plague Commission observed four others. Although, therefore, the occurrence of a primary pest lesion must be looked upon as rare, it is to be noted that the proportion in which certain groups of lymphatic glands are infected is almost directly in proportion to the skin area which is drained by the lymphatics passing to these glands. Thus, the area of skin surface draining into the lymphatic glands of the neck is approximately 1260 square centimetres, that into the glands of the axilla about 3244, and that into the glands of the groin about 6260 square centimetres, the areas having a proportion to each other of about 1 : 1·8 : 5. From the statistics of the Bombay, Punjab, and Karachi hospitals (5442 cases), the proportion of primary cervical, axillary, and inguinal buboes was 1 : 1·3 : 5·8. Even where a primary pest lesion occurs at the point of the inoculation it has frequently been preceded by general symptoms, a point of importance in estimating the manner in which the bacillus invades the body.

Mucous Membranes.—The frequent occurrence of buboes under the chin

and about the angle of the jaw may be taken as evidence that the plague bacillus can penetrate through the mucous membranes of the nose, mouth, or pharynx. The same applies to the conjunctiva. A patient with pneumonic plague accidentally coughed into the eye of a nurse in the hospital at Parel. Conjunctivitis followed, with a plague bubo below the ear on the affected side. A similar case was noted in Hong Kong.

Childe reported the case of a boy who had a lesion on the dorsal surface of the glans penis. Plague bacilli were found in the lesion and in the buboes which developed in both the groins.

In regard to the statement that plague bacilli enter the body through the gastric or intestinal mucous membrane, the Indian Plague Commission were unable to obtain any trustworthy evidence. Feeding experiments have always been found to be uncertain, and it is probable that many animals supposed to have been infected through the stomach or intestine have in reality been infected through the nasal or pharyngeal mucous membrane. Wilm, however, held that the disease could be contracted through the alimentary wall, and Dr. Hunter is of opinion that this is a common method of infection. That in many cases the mucous membrane of the alimentary canal is found post-mortem to be studded with hæmorrhages is, however, no evidence that the plague bacillus gained entrance by this route. In the case of rats, Dr. Klein shewed that in whatever manner the animal is infected, the intestines and mesenteric glands always participate in the disease.

Respiratory Tract (except nose and mouth).—In cases of primary plague pneumonia there can be no doubt that the bacilli may gain entrance by means of the inspired air. Such cases are characterised by great infectivity, and frequently disseminate the disease. This occurred in the laboratory outbreak in Vienna, the attendant Barisch, Dr. Müller, and Nurse Pecha all succumbing to pneumonic plague conveyed from the one to the other. The factors which predispose to the development of lung plague are not fully worked out. From the experiments of Martini it is probable that the bacillus is exalted in virulence in its passage from lung to lung. Other microbes, such as the pneumococcus, may also be associated with the plague bacillus, and possibly affect its virulence.

Escape of Bacilli from the Body.—In ordinary bubonic cases there is usually a short period when the bacilli are shut off from the surface. In a great many cases, however, the blood invasion takes place at a very early date, and from this time onwards the bacilli may escape from the body. By becoming lodged in the capillaries of the skin and mucous membranes, they may make their exit from the body. In the case of the respiratory organs, when there is primary or secondary plague pneumonia they pass out in immense quantities in the sputum. To a less extent this also occurs in ordinary bubonic cases with blood infection. The bacilli may be conveyed to the surface of the intestine and pass out in the fæces, although this has only rarely been demonstrated experimentally. Conveyance of the bacilli to the kidneys and escape by the urine is also proved. In sixty examinations of the urine the Indian Plague Commission found plague bacilli three times. In the case of hæmorrhages from the cutaneous or mucous surfaces of the body the bacilli may make their exit in large numbers.

Infectivity of Patients convalescent from Plague.—The infectivity of plague patients who have recovered from the acute stage of the disease is especially marked in the cases of suppurating buboes, and in cases with bacilli in the sputum or saliva.

It is generally difficult to find bacilli in buboes which have been suppurating for some time. The German Commission had two positive results out of sixteen cases. The Austrian Commissioners were more successful (seven positive in ten cases) in so far that they isolated living bacilli on the nineteenth and twentieth day, and in one case as late as the fifty-second day. Vagedes, in the Oporto epidemic, recovered bacilli from a pelvic abscess two and a half months after the attack of plague was over.

Bacilli may persist in the sputum and saliva of patients for long periods after recovery from plague. Thus in two pneumonic cases, Gottschlich found the bacillus twenty and forty-eight days respectively after the temperature was normal. Vagedes recovered living bacilli from sputum seven weeks after the disease.

Bacteriological Diagnosis of Plague.—During an epidemic of plague in man it may be justifiable to base the diagnosis on clinical evidence alone. In all other cases a bacteriological examination is imperative, and should be conducted by a trained bacteriologist in a suitable laboratory. The diagnosis rests on the demonstration of the bacillus in the suspected material, either by microscopic examination, or in cultures on gelatin or agar plates. Inoculation of the suspected material, or cultures from it, should also be carried out on susceptible animals, such as rats and guinea-pigs. Subcutaneous or intraperitoneal injection is suitable only in cases in which the primary material is not extensively infected with different microbes, or where pure cultures are used. In all other cases the cutaneous application of the infective material is to be recommended. If the accurate diagnosis be of great importance—as is usually the case in non-epidemic periods—several animals should be employed. As death may not take place for some days, it has been suggested that the buboes should be punctured, the juice being examined microscopically or by other tests. The buboes are frequently, however, very small, so that their puncture is by no means easy. It is preferable to kill the animal on the second day, and to dissect out the buboes carefully for further examination.

If there is any doubt as to the identity of the microbe found either in the primary cultures or in the inoculated animals, it should be subjected to all the known tests, including the agglutination reaction with plague immune serum, the suspected case from which the material was primarily obtained being kept under careful observation. In the living patient material may be obtained from the interior of the bubo by

puncture with a sterile hypodermic syringe. In the early stages of the bubo plague bacilli are present in large numbers, whereas later on, especially in the event of suppuration, they may be sparse, and their presence may be obscured by other microbes, which have invaded secondarily. In very severe cases plague bacilli may be obtained in blood-films, and especially in thick drops of blood which have been allowed to dry upon slides. Before staining such preparations it is necessary to get rid of the hæmoglobin by soaking the slides in distilled water. The most certain method of demonstrating bacilli in the blood is, however, to take quantities of 2-5 c.c. directly from the median basilic vein, and to dilute it at once in about 100 c.c. of bouillon. From the mixtures, agar or gelatin plates can then be made. In the case of the sputum in primary pest pneumonia, pest bacilli are usually but not always present in immense quantities, and can often be detected by the microscope alone. Secondary microbes may, however, mask the microscopic picture, and cultures and inoculations must be carried out. In such cases the cultures on gelatin at 20° C. are particularly appropriate, as many of the bacteria which complicate a pest pneumonia do not grow readily at room temperature. In order to save valuable time, cutaneous inoculation directly from the sputum should be employed.

In searching for plague bacteria in urine, this fluid should be collected under aseptic conditions, and it is to be noted that cultures from urine are often slow in growth.

Cutaneous inoculation of the guinea-pig or rat is the only means of satisfactorily demonstrating pest bacilli in fæces, and in any case one must be prepared for frequent disappointments.

Agglutination.—Wyssokowitch and Zabolotny were the first to draw attention to the presence of specific agglutinins in the blood-serum of patients suffering or recovering from plague. This has unfortunately, however, proved a very unsatisfactory test clinically, as the agglutinin formation is usually slight (1:5-1:10), is often late in appearing, and may be entirely absent in cases of undoubted plague. It has also been found experimentally that a great deal depends on the virulence and other characters of the strain of culture used. Where employed, the test should be carried out by the macroscopic method in small tubes, very carefully prepared emulsions of plague bacteria being used.

W. BULLOCH.
S. R. DOUGLAS.

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W. B.

Geographical Distribution of Endemic Plague.—In discussing the existence of plague as an endemic disease, it is necessary to take into account its geographical distribution, and to some extent its history, together with the associated physical and social conditions. The localities where it is now known to occur, or to have occurred within the last thirty or thirty-five years, without being obviously imported from any other centre, are as follows:—

(1) The district of Benghazi (the ancient Cyrenaica), in the province of Tripoli, Northern Africa, last definitely recorded in 1874; perhaps later.

(2) The district of Azir or Assyr, in South-Western Arabia, bordering on the Red Sea, as lately as 1889.

(3) A large area in Asia, comprising Persian Kurdistan and adjacent parts of Persia, Turkish Kurdistan, and parts of Irak or Mesopotamia on the banks of the Tigris and Euphrates, including Baghdad. The chief endemic centre of this area is, according to Tholozan, in the mountains of Kurdistan. From this area it has extented to Northern Persia on the

shores of the Caspian (Resht) in 1877, to Baku on the western, and Astrakhan on the northern shore of that sea; and up the Volga to the village of Vetlanka and its neighbourhood in 1877-79.

(4) The districts of Kumaon and Gurwhal in the north-west of India, on the slopes of the Himalayas, as lately as 1897.

(5) In Southern China, the mountain district of Yunnan, from which epidemics extend to the seaport Pakhoi on the Tonkin Gulf. Apparently by extension from Pakhoi, plague has invaded Canton and Hong Kong in Eastern China, and thence obtained an almost world-wide distribution.

(6) Central Africa, in a district of which the endemic centre appears to lie about Uganda, just under the Equator.

(7) A district of Siberia, in the Trans-Baikal province, where a disease apparently identical with plague is sometimes communicated to man from a rodent animal, the Tarbagan marmot (*vide* p.). It is almost certain that there are other centres of plague in Siberia and Central Asia which cannot be at present clearly defined.

The localities above named appear to be independent endemic centres of the disease since no communication can be traced between them.

These localities are all in the temperate zone, with the exception of the Azir district, which lies just within the tropics, and Uganda, which is just on the Equator; but they have hardly another physical feature in common. Plague prevails in Benghazi on a rocky plateau overlooking a marshy district liable to inundation; on the banks of the Tigris and Euphrates, and on part of the shores of the Caspian in low and marshy situations. But the mountains of Kurdistan are 5000 to 6000 feet high; and the Himalayan seat of the plague approaches 7000 feet above the sea; while in Yunnan the disease is said to occur only at elevations of from 1200 to 7200 feet. These data shew the old belief that plague prevails only in marshy and malarious districts, or has any predilection for the mouths of great rivers, to be entirely unfounded. Indeed the most persistent foci of plague now known are in mountain districts. The social conditions of these regions are, however, more uniform, and will receive special consideration later.

Two Strains of Plague.—Of these endemic seats of plague (1) and (2) are unimportant, while (6) and (7) are as yet imperfectly known. The remaining three only are of importance in relation to the persistence and spread of plague. No. 3 comprises a large district, various parts of which have been frequently visited by plague, but in which the most permanent endemic focus appears to be in the highlands of Kurdistan and part of Persia. It has made frequent extensions into Persia, Armenia, Irak, Turkish Arabia, the shores of the Caspian, and rarely the Black Sea, while in former days it supplied the epidemics of plague in the Levant. For the sake of a name this may be called the Western Asiatic or Levantine plague. (4) and (5), though far apart, may be taken together, since the mountains of Yunnan are an extension eastward of the great Himalayan range, and the disease in these two centres appears to be so identical in its natural history. These two constitute the Himalayan and Chinese, or together the Indo-Chinese, centre. It is the Yunnan plague which has become so widely diffused, not only in the far East, but nearly all over the world, and exhibits, wherever it takes root, the features of the original plague of that region.

It is important to observe that the disease in the two great centres above indicated, and their secondary foci, are not precisely alike, but present variations not constituting two distinct varieties, but different *strains* comparable to the different strains of yeasts which produce different kinds of fermentation.

The Eastern Asiatic strain is distinguished by (1) the frequent occurrence of epidemics of *Pestis minor* or mild plague. (2) The absence of any observed connexion with the epizootic disease in rodents. (3) More frequent self-limited epidemics. (4) Consequently less marked power of extension; for the Eastern Asiatic epidemics have not, in modern times, travelled very far. (5) On the whole less virulence and a lower case-mortality. The mortality at Baghdad and other places in Irak was from 55 to 52 per cent, only in isolated epidemics rising to 90 per cent or more. In Egypt, before the final extinction of plague in the last century, it was as low as 33 per cent. In India, on the other hand, the general case-mortality, according to Dr. Simpson, was 70 to 85 per cent, in Hong Kong 89 to 96 per cent, though in Europeans it was much less; and less also in other countries where the plague has been introduced. (6) The pneumonic form with hæmoptysis is decidedly rare though not unknown. There do not appear to be any marked differences in the symptoms, but the old Western Asiatic plague has not yet been examined with the same scientific accuracy as recent epidemics of the Indo-Chinese plague. At present there are no observations shewing any difference in the bacilli.

The characters of the Indo-Chinese plague are, as contrasted with the other form—(1) An almost invariable connexion with great mortality among rats, and less frequently among other animals. (2) Less frequent occurrence of epidemics of *Pestis minor*, though it is possible that further observation may shew these to be commoner than has been supposed. (3) Remarkable power of extension, as shewn in its spread over a large part of India and conveyance to many other countries. (4) In general, intenser virulence and higher case-mortality. (5) The pneumonic form, accompanied by hæmoptysis is much commoner.

Further observations may shew that some of these points of difference between the two strains are less distinct than they now appear, but the striking contrast in the relation of the two forms of plague to disease in rats will always remain a historical fact, as has been pointed out. These differences confirm to some extent the views of the great epidemiologist Hirsch, who regarded the Indian plague as a variety of the disease distinct from the Levantine or Oriental form, being characterised especially by the occurrence in the former of pneumonia, which he justly remarks is very rarely recorded in the latter form. But after

noting the prevalence of pneumonia and hæmoptysis in the epidemic of Vetlanka, Hirsch abandoned the idea of two varieties of plague, which, however, has still much to be said in its favour. It is important to remember that as the plague now widely distributed over the world is the Yunnan plague, all modern observation and research on the subject since 1894 have dealt exclusively with this variety of the disease.

Endemic Plague in Relation to the Soil.—In places where plague has been long established there are certain relations which connect it with the soil. It persists in certain regions, not distinguished by physical characters from others where it never occurs. Within these regions it will recur year by year or in successive epidemics, at the same spots, even in the same houses. Francis observed at Kumaon two villages on the same mountain, with the same aspect, scarcely 500 yards apart, of which, at every visitation of plague, one always escaped while the other suffered. In cities where a notable part of the population lives on the water in boats and barges, it has more than once been noticed that such persons have entirely escaped the plague. It was so in London in 1665; and also recently in Canton, where 250,000 people live and sleep on the water. Another point bearing in the same direction is the slow pace with which plague spreads on land, quite unlike those diseases like small-pox, measles, etc., which are propagated by contagion passing through the air. Boghurst states that in London in 1665 the plague took six months to pass from Westminster to Stepney through the city. Observations on the occurrence of plague in rats and other animals living under ground, point in the same direction. These and other considerations shew that there is some close connexion of the plague virus with the soil, and the view that plague is originally a 'soil disease' is suggested. This has been the popular belief in many parts of the world, and was dimly perceived by many old physicians (*e.g.* Boghurst in the seventeenth century) though clogged with other quite untenable hypotheses. In the eighteenth century and later the strong belief in contagion banished the soil hypothesis, but observations in India revived it. C. R. Francis explained thus the origin of plague in Kumaon in 1853. Liebermeister suggested that it was probably a 'miasmatic' as well as a contagious disease, and it was provisionally adopted by myself in the *Encyclopædia Britannica* and elsewhere. Dr. Creighton has brought it into connexion with Pettenkofer's 'soil-water' hypotheses. It is not refuted or weakened by the demonstration of the bacillus as the cause of plague, but recent researches make it possible that the virus persists in animals living under ground rather than in the soil itself. The question of the presence and behaviour of the bacillus in the soil under varying conditions is dealt with on p.

Relation of Plague to Climate and Temperature.—Its geographical distribution shews that plague is not exclusively, or even predominantly, a tropical disease. It prevails widely in the temperate zone; even its most permanent endemic seats in India and China, the Himalayan villages and Yunnan, are outside the tropics, and its greatest epidemic prevalence in Bombay, Bengal, and other parts to which it has spread has been on the margin of the tropical zone, a few degrees south of the tropic of Cancer. The presidency of Madras has been conspicuously less affected than other parts of India, and its southern provinces have shewn only a few sporadic, probably imported, cases. The only endemic centres strictly within the tropics are Assyr in Arabia, and Uganda in Central Africa. In South America the places where imported plague has been most conspicuous—Santos, Asuncion, Rosario—are outside the tropical zone. Destructive epidemics have occurred even amid the snows of northern Russia, at St. Petersburg and Moscow. The general conclusion seems to be that while plague may prevail in almost any climate, its seats of predilection are in warm temperate regions, or the borders of the tropical zone. This distribution appears to be determined by the relations of plague to the temperature of the air.

Seasonal Relations of Plague.—In places where plague is endemic, it breaks out from time to time in an epidemic form. The precise laws governing epidemics of plague are not known, but they have an evident relation to seasonal changes. In northern countries epidemics generally begin in the spring, increase during the summer without being checked by heat, and reach a maximum about September. In the winter the disease mostly dies out or lies dormant till the following spring. There have, however, been epidemics which have continued through the cold even of a Russian winter (Moscow, Lower Volga, 1878-79). In Egypt, when the plague was prevalent there, epidemics used to begin in autumn, continuing through the winter, but ending abruptly about midsummer, when the hot winds from the south began to blow. In India the epidemics have mostly begun about October, continuing through the winter, reaching their greatest intensity in March or April, and subsiding in June; so that a comparatively low mortality, but not an actual cessation, occurred in July, August, and September. In Australia the relation of plague to the seasons has been analogous to that in Europe, *mutatis mutandis.*

The general conclusion from these observations is that summer heat in hot climates and winter cold in temperate climates checks or extinguishes plague, temperatures below 50° F. or above 85° being decidedly unfavourable to it. In Mesopotamia a temperature of 86° checks an epidemic, while one of 113° absolutely stops it. In Hong Kong a temperature above 83° caused a decline of the epidemic till the following spring. In Bombay there is a fall in the mortality when the temperature is 82° or even 80°.

In Kumaon, Francis found the epidemic to continue when the temperature was 85° or even 105° in moist air, but a lower temperature would check or stop it if the air were dry. Dr. Simpson states that in Sindh small epidemics have occurred with an air temperature between 110° and 120°, but they are very rare.

Epidemics of plague may last from three to eight months, but the longer period is exceptional. There is no obvious cause except seasonal

changes for the termination of an epidemic. It is remarkable, however, that when the plague begins to decline, its infectivity as residing in houses, bedding, clothing, or other objects which have been in contact with the sick, is rapidly or almost suddenly lost, so that healthy persons may almost with impunity return to infected houses and sleep in infected beds. This was observed in the London Plague of 1665, and also repeatedly in Constantinople, Egypt, and the Levant, when the plague prevailed in those places, as well as at Bombay in 1897-98. No precise explanation can be given of this phenomenon.

Periodical Recurrence of Plague.—While remaining fixed in one spot, plague varies very much in prevalence and intensity. The disease is particularly liable to recur in periodical outbreaks; and in the countries affected popular belief has sometimes assigned a definite number of years, such as seven, for the interval. There is, however, no such regularity; sometimes a great epidemic is followed by several years of apparent immunity, sometimes the disease recurs several years in succession. The interval of apparent health is probably often filled, not so much with sporadic cases of severe plague, as with minor plague.

The causes of the development of minor into severe plague, and of the production of an epidemic, are very obscure. For various reasons it cannot depend upon the number of susceptible persons in the population; the causes must be physical, affecting the biology of the plague bacillus whether in or out of the body. The best established fact is that epidemics in temperate climates have often (but not constantly) been preceded by a long drought. In hot climates, as in Bombay, a recent wet season seems to favour the production of an epidemic. Epidemic diseases among animals, failure of corps, great abundance of lower forms of life—such as flies—and numerous other physical incidents, have been also described as preceding or accompanying plague, but are of little moment. More important are social conditions. Many epidemics of plague have followed on famines, wars, and other calamities, which produce destitution and lowered state of health. Other fevers have sometimes been observed to prevail at the same time.

Conditions favouring the continued Existence of Plague.—It has been seen that no physical conditions, except temperature, have much effect on the prevalence of plague. But certain social conditions have a great influence, and seem almost indispensable to an endemic seat of the disease. The first of these is uncleanliness. All the localities in which plague flourishes are conspicuously filthy. The villages in Mesopotamia were in an incredible state of dirt (Colvill). The sufferers from Indian Himalayan plague were filthy beyond conception (Francis); the habits of the poorer classes of Chinese in Hong Kong and Canton are notoriously of the same kind. A soil contaminated with fæcal discharges and decaying animal matter of all kinds appears to be an essential condition for the vitality of the virus. Among other causes of contamination must be placed cadaveric infection from bad customs of burial. This was notably observed in the Indian seats of plague, where the rocky nature of the soil offers obstacles to efficient burial; in Yunnan also, and formerly in Egypt. Dr. Creighton regards this as the dominant cause, but the general bearing of testimony hardly confirms his opinion. The burial of those who die of the plague among or within dwelling-houses has often, however, been a potent means of continuing the infection; such bodies contain bacilli in enormous numbers, and contagion from dead bodies is undoubtedly possible. Overcrowding of dwelling-houses (not necessarily correlative with density of population) and absence of ventilation are also powerful contributory causes. These conditions are conspicuously prevalent in Hong Kong and Canton; also in Bombay and other Indian cities. But of all social conditions poverty and general social misery seem to be the most influential. The poor are always the chief, sometimes almost the only sufferers, as shewn by such epithets as *miseriæ morbus*, or the "the poor's plague," often given to the disease.

But since destitution and uncleanliness are prevalent in so many parts of the world where plague has never been heard of, these must be regarded as favouring, or perhaps essential, conditions for the disease, rather than as accounting for its origin.

Plague as a communicable Disease.—Unlike true soil diseases—such as tetanus—there can be no doubt that plague is communicable, both from the sick to the healthy, and from an infected place to one previously uninfected; but the extent and nature of this communicability have been the subject of active controversy.

Communication of the ordinary form of plague from the sick directly to the healthy is rare and does not take place especially by contact, as was formerly believed (hence the word contagion, with its false connotations, is better avoided), but by the atmosphere of the sick-room or of the house itself, or by objects in the house; this may be largely, if not completely, obviated by abundant ventilation. It may be difficult to say in some cases whether the infection is acquired from the patient or from the house; but it is pretty clear that communication of plague from one person to another in the open air, or by casual meeting, is very rare, if it ever occur. The pneumonic form of plague, on the other hand, is extremely contagious. The transmission of infection by clothing, bedding, or other objects, that is, in the old phrase, by *fomites*, cannot be questioned though many exaggerated statements have been made on the subject. Recent observations on this subject do not shew merchandise to be an important vehicle for the transmission of plague, except corn, and this only through its association with rats, as was seen in South Africa, at Cape Town, and Port Elizabeth, where the plague was brought by fodder and grain from South America. In Japan infection was traced to bales of cotton. The "gunny bags" used for holding grain were a means of infection in India. In Egypt rags were suspected.

Those who, like the French physicians in Egypt, denied contagion altogether, did so chiefly on the ground of their own personal immunity, though they attended thousands of patients, and performed many post-

mortem examinations. One of them, Bulard, even wore the clothes of a patient who had died of plague, and Clot Bey tried in vain to inoculate himself with matter from a pestilent bubo. But an English physician, White, lost his life by an inoculation experiment. Many similiar negative instances are on record; but much negative evidence is not so conclusive with regard to infection as a few positive cases. On the whole the truth appears to be that during different epidemics and at different stages of an epidemic, plague differs much in its contagious property, as it does in its virulence; so that, broadly speaking, it is highly communicable at some times, and very slightly so, if at all, at others.

In explanation of cases where communication cannot be traced, it should be noted that, besides rats and the like, domestic animals may convey germs of disease. It has been thought that lice, bugs, fleas of various species may convey the infection, but this supposition, though in some cases sufficiently proved, has not been shewn to be the usual or a frequent mode of communication.

Transmission of plague from one place to another not previously infected must also be regarded as well established; though, doubtless, this may have been wrongly assigned as the cause of purely local outbreaks. That this is possible by means of infected ships is clearly proved by the records of the Quarantine at Marseilles (quoted by Prus), when in several instances the infection was, so to speak, caught on the sieve—that is to say, the infected ships gave rise to cases of plague within the quarantine station, of which some were fatal. Of late years numberless instances have occurred of the transmission of plague from Hong Kong and other Chinese ports to many parts of the world, and from the secondary centres thus established back again to Europe and to Africa, so that at the present time this mode of transmission constitutes a serious danger. The most important means of transmission is through the medium of ship-rats affected with plague. Mortality among rats on board ships leaving ports infected with plague has often been observed. In ships thus infected cases of plague have sometimes occurred among the crew or passengers, but not always, for the disease spreads from rats to men only by casual opportunities; but persons employed in unloading the cargo have been infected, and rats leaving the ship have carried the infection inland. By this disease of rats plague has been conveyed on longer voyages and over greater distances than would be possible if the infection were carried by cases of human disease only. For human beings sick of plague would either die or recover before the end of a long voyage. Transmission by land for short and sometimes considerable distances, is also well established. In the London Plague of 1665, towns and villages in communication with London became affected, though they were previously healthy, and had not suffered from plague for many years, if ever. The infection is doubtless generally conveyed by persons either affected with the disease or in the stage of incubation. Such persons convert the house they occupy into a focus of infection, till possibly the virus passes either into the soil directly, or into animals such as rats; and thus a permanent source of infection is established. Conveyance by means of infected objects is doubtless possible, but probably much rarer. In India there were several well-established instances of conveyance of plague to cities and villages by human intercourse quite independently of rats. At Satara the first epidemic was produced by human intercourse alone, whereas in 1898-99 rats were affected before human beings (Thomson). In the Punjab forty-seven out of sixty-three villages were infected by the arrival of infected persons. In some the infection was brought by a single person affected with mild plague (James). But it has happened that the infection thus brought has first fallen upon the rats, and afterwards attacked human beings.

With regard, however, to this mode of transmission, it should be observed that, according to old and sound tradition, the plague does not spread when it is sporadic, but only when it is in an epidemic form. Furthermore its diffusibility varies as much as its contagiosity in the narrower sense, being very marked in great epidemics, very slight or self-limited in others. Many epidemics have burnt themselves out on the spot, or travelled but a few miles; others have spread over whole continents. Generally successive epidemics, if unchecked, cover each time a somewhat wider area.

The rate of extension is also variable, but is generally slow. Plague has taken weeks or months to pass from one side of a city to another; it creeps along from point to point, so as to be compared by some to a drop of oil on paper. Such gradual extension suggests the slow progress of a virus in the soil itself, and probably that is in some places the explanation; but, obviously, only transmission through short distances can be thus accounted for. The migration of rats affected with plague may in some cases be the explanation.

Transmission by the air cannot be said to be impossible, and was once much dreaded; but while this may be possible through distances measured by yards, it can hardly be so through distances measured by miles.

Morbid Anatomy.—Full accounts were made up by the French physicians in Egypt in 1834-35 according to the pathology of that day, and agree in the main with the recent much more elaborate descriptions. A very characteristic feature is that of engorgement and hæmorrhage, the extravasation from the veins affecting nearly every part of the body (Simpson). The bodies of plague patients do not undergo very rapid decomposition, except in the septicæmic form. The central nervous system, especially the brain, is deeply congested; the brain substance in some instances is softened, and the blood-vessels, especially the veins, much engorged. The lungs are much congested, and œdematous especially in their posterior parts, with small hæmorrhages in their substance and on the surface; as well as on the costal and diaphragmatic pleuræ. The larynx, trachea, and bronchi shew catarrhal inflammation, with œdema of the glottis in some cases. Bronchopneumonia is a common complication. It is described by Dürck as

confluent lobular pneumonia or lobular hepatisation. Embolic abscesses are found in some cases. The pericardium contains an excess of fluid, frequently blood-stained, with ecchymoses on both surfaces. The right side of the heart is dilated with black, imperfectly coagulated blood, and the whole venous system is engorged. The veins of the trunk when cut open display numerous small hæmorrhages, which in the vicinity of a bubo become hæmorrhagic patches of considerable size (Simpson). The heart substance is pale, and sometimes softened. The stomach and small intestines may contain blood-stained fluid, sometimes actual blood, the surface shewing intense venous congestion; but Mr. Cantlie, in Hong Kong, found no congestion of these parts. In a few cases superficial ulcerations have been noted. The Peyer's patches are not generally affected, but in some cases are swollen and ulcerated. The large intestine is comparatively normal. The peritoneum is described as shewing great vascular congestion, with hæmorrhages into the mesentery. The mesenteric and retroperitoneal glands are generally enlarged and sometimes shew much inflammation and hæmorrhagic infiltration, which Dr. Simpson says was especially noticeable in Hong Kong. The liver was found enlarged by the French pathologists, sometimes considerably; but Mr. Cantlie found no notable enlargement: its substance is pale and anæmic, and presents the appearance of cloudy swelling. Embolic abscesses may occur (Dürck). Hæmorrhage, interstitial or superficial, is found occasionally. The spleen, according to all observers, is greatly enlarged. The kidneys are sometimes enlarged, and occasionally present hæmorrhagic patches; Mr. Cantlie describes their histological appearance as being that of cloudy swelling. The general appearance is like that of the scarlatinal or septic kidney, and special changes occur in the glomeruli, due to the passage through them of plague bacilli, which are also found in the urine (Dürck).

The one characteristic sign is inflammation and swelling of the internal lymphatic glands, a condition always present even when the external glands are not notably enlarged. All groups of lymph-glands may be affected so as to form continuous chains, the cervical being united with the mediastinal and bronchial; the inguinal with the groups surrounding the iliac vessels and aorta, and with the pelvic glands, and so on. The mesenteric glands are least frequently affected. Agglomerated glands may form masses weighing as much as two pounds. In substance they are sometimes red, congested, and hard, sometimes soft and discoloured, sometimes breaking down into a pulp. The surrounding tissue is infiltrated with serous fluid, and often shews extravasation of blood.

It is evident that, apart from the condition of the lymph-glands and the diffuse hæmorrhage, there is nothing distinctive in the morbid anatomy of plague. Sir T. Fraser remarks that the vascular changes and pervading tendency to hæmorrhage closely resemble the results of the toxæmia set up by certain kinds of snake poison.

Forms of Plague.—It has been generally recognised that plague occurs in two forms distinguished chiefly by their severity, the one having been called *Pestis minor*, or mild bubonic plague, the other, *Pestis major*, or severe bubonic plague, which presents different forms or types. But recent observers prefer to classify the cases under three main heads: viz. Bubonic, Septicæmic, and Pneumonic, according as the glands, the blood, or the lungs are mainly affected. These three forms are not absolutely distinct; they may be combined, or one form may pass into another, but other special symptoms are generally associated with each variety. The mild or minor form seems, however, to deserve special mention, and thus we have four varieties or forms:—(1) Mild bubonic, (2) Severe bubonic, (3) Pneumonic, (4) Septicæmic.

I. **Mild Bubonic Plague or Pestis Minor** has received of late years less attention, because it does not form a part of the severe plague epidemics, and does not seem to be so characteristic a form in Indian or Chinese plague as in the other. But in various parts of the world it has been observed to prevail unchanged for periods of weeks or months. It is often the precursor of severe epidemics, and in such cases the increase in severity is sometimes gradual, but more often a sudden development into the severe form occurs. The bacillus has been found in minor plague by recent observers. This form was observed in Mesopotamia, preceding severe epidemics in the years 1873-77; and in the city of Astrakhan in 1877, the year preceding the severe outbreak of 1878-79 at Vetlanka in that province. It also occurred in London in 1664, the year before the great epidemic. It may also, in plague countries, follow a severe epidemic. This form is distinguished from the severe bubonic form by the facts that it is never, or rarely, fatal; that no contagion is observed, and that it is not transmitted from one place to another, at least *in the same form*. Mild forms of plague have also been observed in India and China prevailing as epidemics, but perhaps with less distinctness than in the Western Asiatic seats of plague. Further observations are, however, required. Since it causes only a slight or no mortality, this form of plague has often been overlooked or misunderstood.

In some countries the prevalence of a disease characterised by glandular swellings without fever has been observed to precede epidemics of definite plague. This happened, for instance, in Egypt 1834-35, where it was explained as due to an *aura pestilentiæ*; in Baghdad 1867, and elsewhere in Mesopotamia ten years later; in Hong Kong and Southern China before the great epidemic (Cantlie). This affection has also been called *febris intermittens bubonica*, but the epithet intermittens is inappropriate. Probably these were all instances of mild plague; but there are no records of examination for bacilli.

II. **Severe Bubonic Plague.**[1]—*Incubation.*—The latent period between the reception of infection and the commencement of symptoms is imperfectly known, but appears to be generally from three to five or at

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[1] In this summary the accounts given by Dr. Cabiadis and Mr. Colvill of plague in Irak have been combined with the more important and more detailed later observations made in India, China, and other parts.

most ten days. Observation for about eight days may therefore be taken as sufficient to shew whether a suspected person is or is not infected, but in some cases this period may have to be prolonged.

The symptoms of plague vary much in their intensity and relative frequency in different epidemics; but the order in which they present themselves and the general course of the attack are tolerably uniform.

Prodromal Stage.—Often the onset is quite sudden; but when preliminary symptoms (prior to the coming on of fever) are observed they are as follows:—The nervous system is chiefly affected. There is severe headache, vertigo, staggering gait, and appearance suggestive of drunkenness passing into lethargy. Colvill says—"The patient appears absent-minded, moves along speaking to no one, enters his house mechanically, shutting the door, and drops on to his bed, as if in despair or wandering in his mind." The pallid face, the injected eyes, the vacant or stupefied expression of countenance, with inability or refusal to answer questions, often enable an experienced eye to make the diagnosis. With these are associated the usual symptoms of acute febrile disease, pains in the limbs, extreme muscular weakness, and intense malaise. The tongue at first is thickly coated on the dorsum, the edges being red; later it becomes extremely dry and of a mahogany colour. Bilious vomiting or hæmatemesis are occasionally the initial symptoms. The prodromal stage, when present, may last a few hours or a day, rarely longer.

Febrile Stage.—Immediately after the above symptoms, concurrently with them, or sometimes from the beginning, high fever comes on, ushered in by a prolonged rigor or repeated shiverings. The temperature may rise rapidly to 102°, 104°, or even to 107° F. and higher. The pulse is always rapid, from 90 to 120 or 130. The maximum is usually attained on the evening of the second or third day; sometimes on the first, rarely on the fourth day. It is described as sometimes very small and thread-like, at other times not especially weak. Mr. Cantlie speaks of it as very variable in force, frequency, and character. The skin is at first extremely dry, not always very hot to the touch. There is excessive thirst, with a sense of burning in the throat and stomach. Constipation is the rule during this stage. Nausea or vomiting are sometimes observed. From the extreme weakness the decubitus is dorsal. The nervous disturbances are mainly those already described; sometimes they pass into active delirium, more often into lethargy and coma. Insomnia may alternate with drowsiness. In children convulsions may occur. Weakness or loss of power of articulation is (according to Dr. Jennings) so constant as to be practically diagnostic of plague. The expression of anxiety gradually gives way to apathy from want of control over the facial muscles. The duration of the febrile stage would appear usually to be from two to five days, but sometimes it is much longer. The fall of temperature is generally described as sudden, and it may not rise again; but in some cases a recurrence of high temperature after three or four days is observed. In some fatal cases the rectal temperature after death was found to be high. In cases which do well there is a gradual but irregular fall, and after fourteen days the temperature is often subnormal.

Buboes or inflammations of lymph-glands constitute the most important and characteristic feature of plague. They are rarely wanting, and then only in cases which are very rapidly fatal; and especially in the pneumonic form, though it is difficult to say in what proportion of cases they are absent, since in the panic of an epidemic they may be overlooked. The term "bubonic plague" is therefore in the main accurate.

Buboes are in some instances the first symptoms to attract the attention of the patient, perhaps by a sudden lancinating pain. More usually they occur after the onset of fever, on the second, third, fourth, or even the fifth day of the disease. With the appearance of buboes there is often some abatement of the fever and general symptoms. The affected glands are generally extremely painful, but sometimes the enlargement is insidious, and only detected on examination. They may enlarge rapidly, more often gradually. Glands are usually affected in groups, but generally one is much larger than the rest. At first the glands are extremely hard, and in fatal or very severe cases may retain this character to the last; in other cases suppuration occurs, which is a late feature and generally regarded as a favourable sign. It is often more prevalent during the decline of an epidemic. On the other hand, rapid softening, flattening, or even disappearance of a bubo during the height of the attack is sometimes observed, and is a sign of the worst omen, being speedily followed by death. It was so in London in 1665, and in later epidemics in Irak. Sometimes the skin over the bubo becomes gangrenous, forming a carbuncle. According to Mr. Cantlie great œdema surrounds the glands, converting the group into an elevated doughy mass, sometimes five or six inches in diameter. A bubo once formed usually lasts during the whole of the attack. In suppurative cases which recover the process may be prolonged for several days, or even for some weeks, and leave formidable scars, the diagnostic marks of a past attack of plague.

The size of a bubo does not generally exceed that of an almond or a walnut, but may attain that of an egg or small orange. Small and hard buboes are regarded as of more serious import than the large and soft. In the majority of cases (three-fourths or more according to some observers) only a single prominent swelling occurs: but swollen glands are to be found in other regions if sought for. Generally about 75 per cent or more of the cases have buboes of some kind. With regard to *situation* all observers agree that the inguinal group of glands is most frequently affected, such cases, according to Cabiadis and Colvill (if with these be included those of the femoral triangle), making 40-50 per cent of the total number; but when the femoral glands have been distinguished from the inguinal, the former appeared to be most frequently attacked. Next in frequency of attack come the axillary glands—in 25 or 30 per cent of cases, and in a larger proportion of female patients; the cervical and submaxillary or other glands are only attacked occasionally. Some

internal glands, especially the various abdominal groups, are always found inflamed on post-mortem examination. In four different sets of observations in India the proportion of inguinal (with femoral) glands affected varied from 63 to 70 per cent, of all cases with buboes. The axillary glands were affected in 15 to 20 per cent, the cervical in 5 to 15 per cent, and in 3 to 5 per cent there was multiple gland affection. The mortality was generally highest in the cases of axillary buboes. It has been supposed that the great liability of the inguino-femoral glands was due to the bacillus entering the skin of the feet or legs in a barefooted population; but this is not confirmed by wider observation. The special liability of this grandular group is the same in every country where plague occurs, whether the inhabitants wear boots or not (Simpson). The situation of the bubo does not regularly correspond with the part where the infection enters the body, though sometimes such a relation is observed. Hence some pathologists hold that the buboes result from a general infection and the distribution of bacilli by the blood. Of secreting glands the parotid is sometimes, though rarely, inflamed.

Carbuncles.—Gangrenous patches of skin, or "carbuncles," though evidently not the same as what are now called carbuncles proceeding from sebaceous glands, form another characteristic feature of plague. According to Cabiadis and Colvill, they occur, however, only in 2 or 2½ per cent of the cases. Red patches appear on the skin, and become indurated and sometimes vesicular; then necrosis occurs, which spreads till the patch may attain a width of some inches. They may occur on any part of the surface of the body, and have sometimes been attributed to direct introduction of the virus of plague into the skin. In recent Indian and Chinese epidemics this feature was distinctly less common than it would appear to have been in the older epidemics.

Petechiæ.—Purpuric patches, due to ecchymoses, sometimes of small size (petechiæ), sometimes larger, are often seen in severe cases. In the seventeenth century they were known as the "tokens," and regarded as invariably indicating the approach of death. Neither petechiæ nor ecchymoses have formed important symptoms in the different outbreaks of the present pandemic, but they are occasionally well marked in severe cases before death (Simpson).

General pustular or vesicular eruptions have rarely been observed.

Sweating is an extremely variable symptom. In certain epidemics very profuse sweats have been observed, in others this feature has been entirely wanting.

Hæmorrhage from various organs is sometimes observed in severe cases, and is much more frequent in some epidemics than in others. Epistaxis is a common form of it, but pulmonary hæmorrhage, usually associated with congestion or pneumonia, is regarded as of specially serious import. It was observed in the first epidemic of the Black Death in Europe (1348), in the epidemic on the Volga in 1879, and on many other occasions. This is characteristic of the pneumonic form of the disease, and was at one time thought by Hirsch to be peculiar to Indian plague. But though apparently commoner in the Indo-Chinese strain, it is by no means confined to that form of the disease.

Hæmatemesis is sometimes so noticeable as to have been called "black vomit"; and intestinal hæmorrhage produces black dejections. Urinary hæmorrhage and metrorrhagia may occur, and the cases are generally or always fatal. The hæmorrhagic form of plague, though not constituting a distinct type, may be compared to the hæmorrhagic forms of small-pox, scarlet fever, and so forth.

The remaining symptoms will be best considered in relation to the various systems of the body.

Nervous System.—The general features have been already described. There is profound poisoning, affecting especially the cerebrum, but with little disturbance of motor function, except occasional convulsions, and the contraction of tendons seen in the last stages of many febrile diseases. Paralysis does not appear in the descriptions except as one of the sequels of an attack. The violent or maniacal delirium of older records has been also noted in recent epidemics. Remarkable cases of this kind were observed in Bombay. Some patients shewed the tendency to leave their beds and rush wildly into the open air, or even attempted to travel to a distance, as has often been observed in typhus and small-pox. In some cases there was a tendency to homicidal or suicidal mania.

Respiratory System.—The respiration is accelerated in the febrile state in proportion to the fever, perhaps more so. In some epidemics marked symptoms of engorgement of the lungs and pneumonia with profuse hæmoptysis are described. These cases are now recognised as the pneumonic form if unaccompanied by buboes. But secondary bronchopneumonia and bronchitis are not unfrequently met with in ordinary bubonic plague. These cases have in some instances given rise to an erroneous diagnosis of epidemic pneumonia. In Hong Kong pulmonary symptoms were absent. These variations are perhaps partly connected with differences of climate and season.

Digestive System.—Beside the condition of the tongue already noticed, some cases give evidence of grave gastric disturbance, in the form of severe bilious vomiting; this is sometimes an early symptom, but it may occur at any stage. The bowels are constipated, as a rule, but profuse diarrhœa sometimes occurs, and has been regarded (Colvill, Cantlie) as a favourable symptom. The occurrence of gastro-intestinal hæmorrhage has already been noted.

Blood and Circulation.—The French physicians in Egypt in 1835-36, a time when bleeding was customary, made some analyses, from which it appears that the blood coagulated imperfectly, and never formed a buffy coat. Its surface presented fatty globules, the serum was deeply coloured, and in some instances the reaction of free sulphuretted hydrogen was obtained. The water was in excess. These results would shew profound decomposition and destruction of red corpuscles. The late Dr. H. F. Müller in Bombay, observed a dark colour and high venosity in

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a drop of blood obtained by puncture when heart-failure was beginning, but no colouring of the serum. Marked leucocytosis has been observed (45,000), and in single cases even 120,000, and 200,000 (Aoyama). The increase affected the polymorphonuclear leucocytes. Alterations in the red corpuscles are not constant. The bacillus is not detected in the blood till the disease is at its height, and is numerous in the later stages only. Cultivation is more successful than microscopical inspection for its detection. Albrecht and Ghon found it in 45 per cent of the cases; the German Commission in a smaller proportion. Cases with bacilli in the blood seldom recover. The *Circulatory* disturbances have been described. The spleen is generally enlarged.

The *Urinary System* presents nothing very notable. The urine is generally diminished, sometimes suppressed; but in the Hong Kong epidemic it was normal. Hæmaturia and albuminuria sometimes occur.

Duration of Attack.—Cases are sometimes fatal within a day, but in general the duration of fatal attacks is three to five days. Colvill, in Baghdad, found that nearly one-fourth of his fatal cases died on the first day, about three-fifths within three days, and five-sixths within five; a very small number of such cases lived over a week. Hence if a patient lived as long as this, he was thought pretty certain to recover. On the other hand, cases in which suppuration of buboes occurs, and which recover, may be protracted to three weeks or a month. Dr. Simpson gives as the result of his experience that death may occur within one or two days or even less, but may be later, from the third to the seventh day, but usually occurs between the second and the sixth.

Mortality.—Plague is the most fatal of all known epidemic diseases affecting large numbers. At the beginning of an epidemic the mortality is often 80 to 90 per cent or more of those attacked, and this rate is maintained or increased at the height of the epidemic. During the epidemic on the Volga in 1879, in one group of villages visited by myself, every person attacked by plague had died. Towards the end of every epidemic recoveries predominate over deaths, so that the average mortality falls; but in some limited epidemics in Irak three-fourths of those attacked have died, and in others the mortality has risen to 90 per cent or more. In the larger epidemics of Baghdad in 1876, the proportion of deaths was officially stated as 55·7 per cent; and at Hillah in the same country it was given by Cabiadis at 52·6 per cent. In other epidemics the percentage of fatal cases has not been more than 40 per cent, and in Egypt in 1834-35 about one-third. In India the general case-mortality has been 70 to 85 per cent among natives. In Hong Kong 89 to 96 per cent of Chinese, but less among Indians (77 per cent) and Japanese (60 per cent) living there. In South Africa for the coloured population 56 per cent, in South America (Asuncion) 50 to 66 per cent (Simpson). The above statistics refer to native inhabitants. The mortality among Europeans was much less. In Hong Kong it was 34·6 per cent; in Bombay 30 to 40 per cent; in Cape Town 33·3 per cent.

Our Australian colonial populations have shewn a mortality of 31 or 32 per cent of the cases.

The total mortality has notoriously been in many instances very great both absolutely and in proportion to the population, though older accounts may have been exaggerated. The Black Death is calculated to have carried off one-third of the inhabitants of Europe, and in some countries more than one-half, but these estimates must be uncertain. In modern times it is said that the plague of 1830-31 killed 60,000 of the 150,000 inhabitants of Baghdad. The epidemic of 1876 in Irak is stated to have destroyed one-eighth of the whole population. In 1881 most of the villages affected lost a moiety or more of their inhabitants. As in such times a large part of the surviving population seeks safety in flight, it is easy to understand how villages may be entirely ruined and depopulated by the ravages of plague, as was the case also in our own country in the fourteenth century. The mortality in India has been noticed on p.   .

III. Pneumonic Form, or Primary Plague Pneumonia.—The form has been observed at various times, as in the first epidemic of the Black Death in 1348, in the Pali Plague 1838, and other Indian epidemics, and at Vetlanka, Russia, 1878-79. Forbes gave a clinical description of cases in Pali 1838, of which the late Dr. H. F. Müller said that, apart from some details, there was nothing to add, nor anything to take away. Pneumonic plague was, however, first discriminated as a special form by Dr. L. F. Childe at Bombay in 1897, from cases most of which had been diagnosed during life as pneumonia, not plague. It should be remembered that bronchopneumonia of greater or less severity is a not infrequent complication in bubonic plague, and is distinguished as *secondary pneumonia.*

Symptoms and Clinical Course.—The attack begins usually with one violent rigor, or repeated shivers, but these may be wanting. There are no prodromal symptoms. Headache, giddiness, vomiting, variable in intensity, follow. There is no primary bubo. The facial expression is one of great anxiety and there is imperfect articulation as in the bubonic form. Pleuritic pain may be felt on the second, third, or fourth day; cough, with expectoration, and râles heard on auscultation may commence on the third, fourth, or fifth. The temperature is high, but does not differ specially from that in other forms of plague. The prominent symptoms are cough and blood-stained expectoration. Sometimes, but not always, marked hæmoptysis and excessive dyspnœa with a tendency to cyanosis. The respiration rate, according to Müller, was as a rule over fifty, sometimes rising to seventy-five. The auscultatory signs are those of lobular pneumonia. The dullness on percussion is not marked. The sputa have no characteristic appearance, but are found to contain bacilli in enormous numbers. These are also detected in the blood. Swelling of the spleen is very marked. Death occurs from failure of the heart. In the older accounts death is said to have occurred within two days. At Bombay about half the cases were fatal within five days, but some

were prolonged to a week or more. The disease is almost invariably fatal.

Pneumonic plague is highly contagious and generally reproduces the same form; this was the case in a series of eighteen cases observed at Bombay. Sometimes by accidental inoculation the bubonic form results. In one case at Bombay a portion of sputum falling on the conjunctiva gave rise to ordinary bubonic plague.

Post-mortem examination shews, besides the signs of scattered foci of pneumonia in the lungs, inflammation of the bronchial glands.

IV. Septicæmic or Septic Form.—This is an extremely virulent and rapidly fatal form of plague, in which, as in the pneumonic, buboes are absent, or not discovered during life. Some observers do not recognise it as a distinct form. It is distinguished by the large number of bacilli circulating in the blood and by clinical characters.

The attack begins, as in other forms, with rigors, headache, vomiting, and high fever. In some cases the temperature is below 100° F. (Simpson). The implication of the nervous system is very marked. "Extreme nervous prostration, weakness, drowsiness, restlessness, hurried and panting respiration, small and full pulse, tympanites, delirium, picking of the bed-clothes, stupor, and coma quickly follow." There may be bleeding from the nose, kidneys, and bowels. Death may occur on the first, second, or third day, with symptoms of collapse. If the patient survive longer buboes may appear. In fatality this comes near to the pneumonic form.

Prognosis.—The most unfavourable symptoms are hæmorrhage, in whatever form, and petechial eruptions or "tokens"; both affections are generally lethal prognostics. Profound affection of the nervous system is also an unfavourable sign, and so is abundance of bacilli in the blood. Suppuration of buboes is always of good omen. Sex and age appear to have little or no influence on the result. All observers agree that prognosis is generally very uncertain, and that cases apparently mild often terminate fatally.

Diagnosis.—Absolute diagnosis is best made, when practicable, by the detection of the bacillus in the tissues or fluids of buboes or other parts. But when this is not possible, there are other signs which may be sufficient for diagnostic purposes. No acute febrile disease presents the peculiar affection of the lymph-glands. Nevertheless a casual lymphatic inflammation or an inflamed parotid gland may occur in rare cases of other diseases, especially in typhus, which was at one time thought to shew in some cases a transition to plague. Modern observers, however, have found no difficulty in making the diagnosis; the longer duration of typhus ("the fourteen days' fever") and the collective symptoms making a well-marked distinction. Malignant forms of malaria have sometimes been confounded with plague; but the absence of intermissions, or even of definite remission of the fever, and the inefficacy of quinine, are obvious distinctions. The aspect or facies of a malarial patient is also very different. But if suspicion has not been aroused, mistakes in diagnosis are frequently made; and at the beginning of an epidemic the disease has been often, not to say generally, unrecognised. The chief points to be attended to, apart from glandular enlargements, are—the sudden onset, the high temperature with dry skin; character of the tongue and injection of conjunctivæ; intense headache, insomnia, delirium, and sometimes vomiting; the peculiar facial expression above mentioned; peculiar manner, refusal to answer questions, and (as some say) disinclination of the patient to allow that he is ill.

Treatment.—The treatment of plague cannot be regarded as satisfactory, but the newer method of serum treatment is more promising than the merely symptomatic therapeutics formerly adopted. In old days opinions were divided as to the value of bleeding, but the balance of experience was decidedly against it. The violent sudorifics used in the seventeenth century appear to have been useless.

In modern times quinine has naturally been largely administered, but the general testimony is that it is quite useless. Antiseptics (such as carbolic acid, salicylic acid), antipyretics, and cardiac stimulants have all been tried with no better results; purging with calomel and magnesia was largely used in Hong Kong, but with little benefit. In fact, nothing approaching to a specific or antidote in the way of drugs has ever been discovered. The general principles of treatment would seem to be, as in other asthenic fevers, to give the patient an abundant supply of fresh air, to avoid overcrowding, to use cold affusions or baths in the height of the fever, and to administer such cooling or other drinks as may promote his comfort. When the strength is failing, stimulants are of course indicated, but alcoholic stimulation appears to be of less value than in typhus. In the seventeenth century some good observers denounced the use of "strong waters" as positively pernicious. Hypodermic injections of strychnine have been largely employed, and with good effect. Digitalis and strophanthus are recommended to sustain the force of the heart. In a malady of such short duration the utility of abundant nutrition would appear to be of less importance than in more protracted illnesses One of the most important factors in assisting the patient's recovery, as well as in preventing contagion, is abundant, or even superabundant, ventilation, the good effects of which are well known in the treatment of typhus.

Major Thomson and Dr. Thomson, in their treatise on plague, lay great stress on keeping the patient prone till the temperature has been normal for at least four days. "Injudicious breach of this rule, by allowing patients to sit up, led to the death by syncope of twenty convalescents."

The local treatment of the buboes has received much attention. The general result of experience is that energetic treatment by caustics, mercurial inunction, or early surgical interference, is painful and fruitless. In early stages soothing applications only, such as poultices, anodynes, or ice-bags, should be used. When softening or suppuration occurs, surgical treatment by incision and drainage is called for, but nothing is

gained by too early incision (Simpson). There is no evidence of the value of thorough antiseptic surgical methods; but in the Hong Kong epidemic the injection into the glands of solutions of perchloride of mercury and carbolic acid seemed to be of temporary benefit.

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Specific Prophylaxis and Cure.—The basis of the attempts to immunise human beings against plague is the oft-repeated observation that recovery from an attack of the disease confers immunity, although the individuals continue to be exposed to infection. This observation has been utilised in the employment in pest hospitals of nurses and attendants who have had the disease (Netter). The immunity, however, is not absolute, as in many epidemics it has been noted that patients may succumb to a second attack of plague after successfully passing through a first. Thus several cases were submitted to the Indian Plague Commission, in which two and even three attacks had occurred in the same person, the intervals between the attacks varying from eight days to twenty-six months.

The artificial establishment of immunity against plague may be brought about, as in certain other infective diseases, in two ways. (A) Active immunisation, by the inoculation of cultures of the plague bacillus or its products. (B) Passive immunisation, by the inoculation of the blood-serum of animals which have undergone active immunisation. Some observers recommend a combination of these two methods for use in man.

A. *Active Immunisation.*—This has been practised in India on a very large scale, and we are in possession of a large number of facts dealing with this question. In general, the active immunising agents used in connexion with plague may be divided into four groups, viz. (1) the inoculation of cultures (broth or agar) which have been heated so as to destroy the vitality of the plague bacillus. This is the basis of the vaccins used by Haffkine and the German Plague Commission; (2) inoculation of products prepared directly from cultures of plague bacilli (Lustig and Galeotti's vaccin); (3) inoculation of products derived from the bodies of animals recently inoculated with living plague cultures—*e.g.* Terni and Bandi's vaccin. Hueppe and Kikuchi's vaccin, Klein's prophylactic; (4) inoculation of living cultures attenuated spontaneously or artificially—*e.g.* Kolle's vaccin.

As the active immunisation by killed cultures is the only one which has been applied to man on a large scale, it will be necessary to refer to it in detail. The immunising value of dead cultures of *Bacillus pestis* was first observed by Yersin, Calmette, and Borrel in the case of rabbits which were found to withstand doses of living virulent plague cultures, provided that they had previously been treated with agar cultures heated to 58° C. The experimental results gained by these investigators were then applied to man by Haffkine in his plague prophylactic. In the preparation of this agent broth-cultures inoculated with plague bacilli are grown for one month, and after testing their purity, the bacilli are destroyed by heat at 65° to 70° C. As a further precaution a quantity of carbolic acid is usually added. From the first, great difficulty was experienced in adequately standardising the vaccin, so that the dose was more or less arbitrary, and varied in different samples between 5 and 20 c.c. With a vaccin prepared as above Haffkine first of all inoculated himself (10th January 1897), the resulting symptoms being severe pain, tenderness, fever, and considerable malaise. Almost immediately after this experiment large numbers of people in India availed themselves of the protection assumed to be afforded by the plague prophylactic, and the earliest results were strongly in its favour, for of 8142 persons inoculated in Bombay only eighteen developed plague. Before, however, dealing with the statistical data on which the true value of Haffkine's vaccin is based, it is necessary to consider the questions of its dosage, standardisation, and the results that have been determined experimentally in the case of animals. Even at the present time considerable doubt exists as to whether the immunising principle of Haffkine's vaccin is contained in the fluid part, in the sediment, or in both. Contrary to the opinion of Kolle, Liston, and others, Dr. Klein (141) found that the fluid part of the vaccin is endowed with protective properties. In Captain Douglas's recent experiments with the filtrates from seven different vaccins, 52·5 per cent of the rats immunised with the filtrates survived lethal doses of living plague bacilli administered at the end of ten days. It would appear also that the degree of virulence of the plague culture is not a matter of great moment in the manufacture of the prophylactic, as Captain Douglas obtained a high degree of protection from vaccins prepared from cultures which were practically non-virulent. Haffkine judged the strength of his vaccin and the dose to be employed by the degree of opacity which it presented to the naked eye, or in its first inoculations by the equally unsatisfactory method of determining the dose necessary to produce a certain rise of temperature when injected into human beings. In his evidence before the Indian Commission, Captain Douglas shewed that the amount of sediment was sometimes seven times as much in some vaccins as in others. Even at the present time, however, the difficulty of standardisation has not been surmounted, and it would seem that the only feasible method is to inoculate comparative groups of human beings with varying doses, and to determine which dose leads to a maximum production of anti-bodies in the blood, or which dose leads to the greatest protection when the inoculated individuals are exposed to the natural risks of plague infection.

The effects of the inoculation of Haffkine's vaccin can only be described as severe. Three hours after inoculating himself with a dose of 1 c.c. of a six-weeks-old dead broth-culture, Captain Douglas was seized with a rigor; considerable febrile disturbance lasted for several days, accompanied by great malaise and pain at the point of the inoculation. To what extent these unpleasant symptoms are a necessary part of a successful plague vaccination is not known.

Results obtained in India by the use of Haffkine's Prophylactic.—Although the methods of standardising the vaccin were crude, and although it was frequently contaminated by extraneous microbes, the Indian Plague Commission, after a searching inquiry into the whole question, reported favourably on Haffkine's method of active immunisation. The conclusions of the Indian Commission gave a considerable impetus to the practice of inoculation, and large numbers of people were inoculated when plague spread into the Punjab. Unfortunately a disaster occurred at Malkowal in November 1902, when nineteen people, inoculated from the same bottle of vaccin, were attacked with tetanus and all succumbed. This, combined with racial prejudices, has done a great deal to thwart the progress of plague vaccination. In reference to the value of the statistics, it was considered by the Commission that the following series of inoculations were the least fallacious, viz. those at the Byculla house of correction, at Umarkhadi, Undhera, Bangalore, Bulsar, Lanauli, Kirki, Gadag, and Daman. In the subjoined table the total results have been worked out from data given by the Commission.

	No. of Cases Inoculated.	Cases of Plague.	Per cent of Plague Cases.	Deaths from Plague.	Per cent of Deaths from Plague.	Case-Mortality per cent.
Uninoculated . .	11,272	469	4·16	348	3·08	74
Inoculated . . .	15,082	342	2·26	147	0·98	43

Taking all the facts into consideration, the Indian Plague Commission arrived at the following conclusions: (1) "Inoculation sensibly diminishes the incidence of plague attacks on the inoculated population, but the protection afforded against attacks is not absolute. (2) Inoculation diminishes the death-rate among the inoculated population. This is due not only to the fact that the rate-attack is diminished, but also to the fact that the fatality of the attack is diminished. (3) Inoculation does not appear to confer any great degree of protection within the first few days after the inoculation has been performed. (4) Inoculation confers a protection which certainly lasts for some considerable number of weeks. It is possible that the protection lasts for a number of months."

With a properly standardised and sterile vaccin, and with a dose accurately determined to be the optimal one, very much better results might be expected.

Other Vaccins.—The difficulties of standardising Haffkine's prophylactic, and also the severe effects induced by its inoculation, led the German Plague Commission to recommend the use of killed agar cultures. Experimentally a vaccin made in this way gives good protection, but it has not been extensively used on man. Lustig and Galeotti isolated a nucleo-proteid immunising substance from plague cultures by digesting the bacilli with potash and then precipitating with dilute acetic acid. The precipitate is then dried and constitutes the vaccin. For an adult the dose is stated to be 2 to 3 mgr. This vaccin was employed to protect 600 people in San Nicola (La Plata), and no one contracted plague. Shiga recommended protection by a combined use of anti-plague serum and heated agar cultures, this method being employed in forty-seven cases in Osaka and Kobe. Besredka made a vaccin by first digesting the bacilli with saline solution and subsequently precipitating the bacillary bodies by a strong agglutinating serum.

Both the German and Austrian Plague Commissions pointed out that living cultures which had undergone attenuation might be used as vaccinating agents. In 1902 Kolle and Otto made a large number of experiments with an old living laboratory culture which had undergone attenuation, and reported very successful results concerning the immunisation of guinea-pigs. Thus, of thirty-four guinea-pigs inoculated with the attenuated culture, 76 per cent survived the introduction of virulent cultures at a subsequent date. Recently Kolle and Strong have reported the results obtained by inoculating living attenuated cultures in human beings. The cultures were so attenuated that an entire agar slant culture would not kill a guinea-pig. The first injections were carried out in the Philippines by Strong on prisoners under the sentence of death, $\frac{1}{100}$ of a loopful of living bacilli being inoculated under the skin without appreciable effect. Later it was found that a whole agar culture could be inoculated without any severe reaction. Of forty-two human beings inoculated in this way it was noted that the temperature begins to rise a few hours after inoculation, occasionally reaching 104° F. By the third day the temperature falls; the local lesions are slight. The degree of protection afforded by vaccinating human beings with living cultures has not yet been determined, but from similar experiments on monkeys and guinea-pigs it may be expected to be high. Naturally, very great care would be necessary in recommending a method like this on a big scale in plague-stricken communities, as from unforeseen circumstances the virulence might increase and plague be induced. As long ago as 1755, Weszpremi suggested the artificial inoculation of pest on the lines of variolisation, and in 1781 a Russian physician, Samoilowitz, inoculated himself with plague pus: he passed through a mild attack of bubonic pest and became immune. He recommended the application to the unbroken skin of a pledget of lint saturated with bubonic pus. Other experimenters had, however, very unfortunate results. Thus Cerutti inoculated six persons, five of whom died of pest.

Terni and Bandi have prepared a vaccin from the peritoneal exudate of animals inoculated with living virulent pest cultures. Immediately after the animals succumb the peritoneal exudate is collected and incubated at 37° C. for twelve hours. The vitality of the contained bacilli is destroyed by heat at 52° C., and the fluid is then diluted down

with water containing carbolic acid. This vaccin is said to have good immunising powers. Hueppe and Kikuchi have recently described a somewhat similar method depending on the presence of aggressins obtained by the method of Bail. On the same principle is the new plague prophylactic advocated by Dr. Klein (142). This is prepared from the necrotic plague nodules in the buboes and spleen by drying over sulphuric acid at 46° to 47° C. until complete sterility is obtained. 10 to 15 mgr. of the dry powder suffice to protect rats against virulent plague bacilli.

B. *Passive Immunisation—Anti-plague Serum.*—Following the lines laid down by Behring and Kitasato for diphtheria and tetanus, Yersin, Calmette, and Borrel immunised horses with plague cultures, and asserted that after a time the serum acquires antidotal properties preventing or curing a pest infection in animals. In general, two types of anti-plague serum may be recognised, viz. one derived from the inoculation with cultures of plague bacilli (Paris serum, Berne serum, Lister Institute serum, Brazil's serum), and one derived from the inoculation of animals with nucleo-proteids produced from cultures (Lustig's serum). In the former of these horses are treated first with killed then with living cultures in doses gradually increasing till quantities as large as 100 c.c. can be tolerated without danger. At first the inoculations are made subcutaneously but afterwards intravenously. The horses are bled about three to four weeks after complete recovery has been established. Apart from determining whether the serum is toxic, accurate standardisation does not appear to be carried out, the dose recommended for man being entirely empirical. Since small doses failed, larger doses have been tried, and in India, in accordance with Roux's recommendation, an initial dose of 100 c.c. was used. Quantities up to 235 c.c. (Walton and Douglas), and in one case 700 c.c. (West), were given but failed to prevent a fatal issue. Apart from the ordinary effects witnessed on injecting alien serum, no serious complications occurred. In regard to the experimental evidence of the protection afforded by plague serum, Koch, v. Behring, Pfeiffer, Kolle, and Martini found that it could prevent a fatal issue, provided it were inoculated first. Whereas, if living virulent plague bacilli were injected at the same time as the serum, the latter was practically valueless, and still less so if the plague culture were injected first. As has been observed in man, the serum, however, appears to prolong life.

Results in Man.—In India Yersin obtained relatively favourable results, as did other observers, when selected cases only were treated. Wherever cases have not been selected and a series of strict controls have been taken, practically no advantage has been seen in the serum group. Thus in the cases treated by Captains Douglas and Walton the following were the results:—

1. Bangalore.

	Cases.	Deaths.	Case-Mortality.
Treated with serum . . .	49	31	63·2
Treated without serum . .	54	29	53·7

2. In Bombay every second case was treated with serum, the others serving as controls. In this series the cases were strictly comparable both as regards severity of type and period of disease.

	Cases.	Deaths.	Case-Mortality.
Treated with serum . . .	28	24	85·71
Treated without serum . .	28	23	82·14

In the entire series of cases (treated with Paris serum) in which reliable controls existed, Captains Walton and Douglas had the following experience :—

	Cases.	Deaths.	Recoveries.	Case-Mortality.
Treated with serum . .	226	168	58	74·83
Treated without serum . .	231	163	68	70·56

The exhaustive analysis of all the available data compelled the Indian Plague Commission to the conclusion that the "method of serum-therapy as applied to plague has not been crowned with a therapeutic success in any way comparable to that obtained by the application of the serum method to the treatment of diphtheria." Still more recently Colonel Bannerman (118) has analysed the results obtained in India up to May 1904, and has also come to the conclusion that anti-pest serum is much less efficacious than diphtheria antitoxin. The following table, taken from Colonel Bannerman's paper, refers only to cases "in which the conditions of trial were reasonably accurate, and in which a series of control patients strictly comparable with those treated with serum was available."

	Serum Cases.				Control Cases.			
	No.	Deaths.	Recoveries.	Case Mortality per cent.	No.	Deaths.	Recoveries.	Case-Mortality per cent.
Roux-Yersin serum by Indian Plague Commission (Bangalore)	49	31	18	63·26	54	29	25	53·7
Roux-Yersin serum by Indian Plague Commission (Bombay)	28	23	5	82·14	28	24	4	85·7
Roux - Yersin serum by Russian Commission (Parel)	50	40	10	80·0	50	40	10	80·0
Roux-Yersin serum by Dr. Mayr, 1902	31	29	2	93·54	31	29	2	93·54
Roux-Yersin serum by Dr. West (Bombay)	68	45	23	66·17	68	41	27	60·29
Total treated with Roux-Yersin serum	226	168	58	74·33	231	163	68	70·56
Lustig's serum (Dr. Turkhud, 1900)	66	54	12	81·81	66	48	18	72·72
Lustig's serum (Dr. Mayr, 1902)	31	31	...	100·0	31	29	2	93·54
Lustig's serum (Poona, 1902)	27	21	6	77·7	28	20	8	71·42
Lustig's serum (3rd series, Bombay)	484	330	154	68·18	484	385	99	79·54
Total treated with Lustig's serum	608	436	172	71·71	609	482	127	79·14
Terni's serum . . .	110	89	21	80·90	110	90	20	81·81
Brazil's serum (Maratha Hospital)	50	41	9	82·0	50	45	5	90·0
Brazil's serum (Modikhana Hospital)	20	17	3	85·0	20	15	5	75·0
Total treated with Brazil's serum	70	58	12	82·85	70	60	10	85·71

While the serum is unable to influence the case-mortality in any marked degree it would appear that life is frequently prolonged by its use as is seen in the following table also taken from Col. Bannerman (118).

Kind of Serum Used.	Average Number of Days in Hospital in Fatal Cases in		Advantage in Favour of Serum Cases.
	Serum Cases	Control Cases.	
Roux	7·57	4·19	3·38
Lustig	3·89	2·76	1·13
Terni	3·27	2·93	0·34
Brazil – Maratha Hospital	2·56	2·25	0·31
Brazil – Modikhana Hospital	2·06	4·61	−2·55

It would also appear probable that intravenous are more beneficial than subcutaneous injections of the serum, as the absorption by the latter route is much slower.

	Serum Cases.			Control Cases.		
	No.	Deaths.	Case-Mortality per cent.	No.	Deaths.	Case-Mortality per cent.
Subcutaneous injection only	43	29	67·4	43	28	65·1
Subcutaneous injection followed by intravenous injection.	12	8	66·6	12	6	50·0
Primary intravenous injection followed by similar injections or in some few cases by subcutaneous medication.	13	8	61·5	13	7	53·8
	68	45	66·2	68	41	60·3

Mode of Action of Antiplague Serum.—Considerable doubt exists whether antiplague serum possesses bactericidal properties or not. According to Kolle slightly virulent plague bacilli are dissolved by the serum *in vivo.* Sir A. E. Wright and Captain Windsor were unable to demonstrate any bacteriolytic action in normal serum *in vitro.* Markl attributes the action of plague serum mainly to phagocytosis, and in conformity with this observation Captain Douglas found that after inoculation of Haffkine's vaccin the opsonic index of the serum rose to three times the normal strength, but fell away after the ninth day. Markl also attributes antitoxic properties to antiplague serum. Under the influence of injections of plague cultures

agglutinins are developed in the serum, and if plague serum be added to filtrates from plague cultures, an abundant development of *precipitins* can also be seen.

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W. B.
S. R. D.

Prophylaxis and Prevention of Plague.—The measures comprised under this head have for their object (*a*) to prevent the transmission of plague from one place to another; (*b*) to prevent the spread of plague, when the disease, or its germs, have been introduced into any place; (*c*) to remove or modify local conditions which make the place a favourable soil for the growth of either endemic or imported plague.

(*a*) Regulations intended to secure the first of these objects have been known and practised for centuries. Since it was long ago observed that sick persons or contaminated objects might carry the infection, the rough method of total exclusion was adopted to prevent transmission of the disease. But when it was found that this practice involved complete stoppage of trade and intercourse, and was, moreover, not always effectual, the attempt was made to permit intercourse under such conditions that the infection should be kept out. The measures founded on this principle constitute what is strictly called *quarantine.* The system thus called was framed by the Venetians about the year 1485, with a reference to sea traffic, especially to their trade with the Levant; and was the model for all the similar regulations which governed European trade for centuries; being applied, with necessary modifications, to land traffic also. It remains a marvellous product of Italian ingenuity; such faults as it had being due to imperfect knowledge, or to mistaken principles. The system consisted in careful examination of all ships coming from infected or suspected countries; the detention of those to which any suspicion attached, and the removal from them of all persons and merchandise to

strictly isolated buildings called Lazarettoes, where they were detained for forty days. During this time the passengers were carefully watched for the appearance of any symptoms of illness, while all merchandise, personal effects, and clothing were submitted to a minute process of disinfection by exposure to air and sunlight. If any case of plague occurred, the period of forty days had to be begun afresh. The system is now obsolete, and need not be minutely described; but there can be little doubt that while it was in force it was, though not always successful, even in Venice, largely efficacious in preventing the introduction of plague from the Levant into European ports. At Marseilles, for instance, there were several instances of plague being arrested in the quarantine station, and not spreading into the town: though on the memorable occasion of 1720 these precautions failed, and plague forced the barriers, producing a celebrated epidemic. In other Mediterranean ports, immunity was secured for many years. The old quarantine system was an international arrangement secured by treaties, and was not formally abolished till 1897. In England it cannot be said that any quarantine system was ever regularly enforced; the policy in regard to plague oscillating between extreme laxity and the temporary enforcement of total stoppage of traffic. A very rigorous system recommended by Mead in 1720 never had to be put into practice. The first Act of Parliament establishing a general quarantine system was the outcome of a Parliamentary Commission in 1819, at which time it was hardly needed. The system was finally abolished in 1897 by the repeal of that Act.

To prevent the spread of plague on land the old custom, which lasted up to the last few years, was to surround the infected town or district with a military *cordon*, which persons were prohibited to cross under pain of death. In the eighteenth century some people were actually shot for breaches of these rules.

International Agreements as to the Prophylaxis of Plague.—The regulations now in force are based upon the decisions of the International Sanitary Conventions, held at Venice in 1897 and at Paris in 1903, regarding cholera and plague. The later Convention added certain regulations as to the destruction of rats on infected or suspected ships. The chief provisions agreed to at these Conventions are:—(1) That every Government must immediately notify to the other Governments the first appearance of recognised cases of plague in its territory; and, beside other details, the presence of that disease or of unusual mortality among rats and mice. (2) When several non-imported cases of plague have occurred in a certain place, that local area shall be declared infected; and the Government of that country shall take measures to prevent the spread of the epidemic. Other Governments may adopt any measures they think proper with regard to arrivals from an infected area or country, but must immediately make these arrangements public. (3) To prevent exportation of plague from infected ports there must be medical inspection of the crew and passengers of outward-bound ships, detention of persons with suspicious symptoms, and disinfection of suspected articles. (4) To prevent importation of plague by ships from infected ports, special measures are authorised. After medical inspection such ships are declared *healthy*, if they have left the infected port for ten days or more and plague has not appeared. If cases of plague have occurred on board, but not within twelve days, such ships are declared *suspected*. If plague has occurred on board within twelve days, the ship is *infected*. These are differently treated. *Healthy* ships are subjected to no restrictions; but the crew and passengers are placed under surveillance for ten days from the date of leaving the infected port; that is, their names and destinations are recorded, and information is given to the health authorities of the places to which they are going. In *suspected* ships those parts of the ship exposed to infection must be disinfected, and the persons are kept under surveillance for five days from the date of arrival. Destruction of rats on board is recommended. In the case of *infected* ships, the sick are at once disembarked and isolated; other persons are isolated for five days, and kept under surveillance for ten days, at the discretion of the authorities. Those parts of the ship which have been infected by plague-patients must be disinfected, and baggage and personal effects also, at the discretion of the authorities. Rats on board must be destroyed as quickly as possible; and, in any case, within forty-eight hours. Even a healthy ship in which rats affected with plague have been found, or where there has been an unusual mortality of them, is subject to similar rules for destruction of rats, disinfection, and surveillance of persons.

Land Quarantine.—The regulations for quarantine on land frontiers are much simplified. The old system of "Sanitary Cordons," intended to prohibit all communication with an infected place, is now recognised as useless, and as having special dangers of its own. But there is to be medical inspection at the frontier of all travellers, with detention of sick or suspicious cases, and disinfection of personal effects belonging to such persons. Merchandise, in general, is not subject to detention, but exclusion or compulsory disinfection may be applied to certain articles of personal use, such as rugs, clothing, bedding; and to raw hides, animal refuse, hair, and the like. Postal traffic is not interfered with. Special regulations were made by the Paris Convention of 1903 for traffic through the Red Sea and the Suez Canal, and for pilgrimages to Mecca, which need not be considered here.

Preventive Measures against Plague in the United Kingdom.—The regulations now in force, under the authority of the Local Government Board, against the introduction of plague are based upon the decisions of the International Sanitary Conventions, and were summarised as follows, by the late Sir Richard Thorne[1]:—(1) Medical examination of

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[1] "Reports and Papers on Bubonic Plague, issued by the Local Government Board, 1902," p. 34. The complete regulations may be found in the same volume.

all persons on board ships arriving from infected or suspected ports; (2) Removal to an isolation hospital of any person suffering from plague, or suspected plague; (3) Disinfection of articles believed to have had opportunity of becoming infected; (4) Disinfection of those parts of the vessel occupied by the case of plague, or suspected plague; (5) The taking of names and addresses of all persons, including the crew, on board ships where plague, or suspected plague, has occurred; such persons being at liberty to proceed to their destinations; (6) Transmission of these names and addresses to the sanitary authorities of the respective districts concerned, with the view that these newly arrived persons be kept under the supervision of the Medical Officer of Health for ten days. The enforcement of these precautions is directed by several memoranda issued by the Board. A supply of Haffkine's prophylactic is kept in readiness by the Board, to be supplied to any medical officer of health who may require it. Arrangements have been made for testing by a bacteriological expert, appointed by the Board, the diagnosis of any plague cases that may be reported.

A special memorandum refers to *Ship-borne Rats and Plague*, of which the following are the chief heads:—(1) On the arrival of a vessel whereon plague, or suspected plague, has occurred, methods should be taken to destroy the rats on board the vessel. Until this has been done, endeavour should be made to prevent rats leaving the ship by mooring the vessel in an isolated position, and by placing guards on cables and hawsers used for mooring purposes. (2) In the case of vessels arriving from infected places, even if no plague, or suspected plague, have occurred, strict inquiry should be made as to mortality or sickness among rats during the voyage. The body of a sick rat should be obtained, in order to ascertain, by bacteriological examination, the nature of the malady affecting them. (3) Exceptional sickness or mortality on board of any vessel arriving in the district, from whatever port, should be viewed with suspicion. (4) Rats, when destroyed, should not be handled, but cremated. (5) In the event of the ship-rats being found to be infected with plague, all parts of the vessel frequented by those animals should be disinfected. (6) The authorities of seaport towns invaded by plague should endeavour to secure the destruction of all rats in the town, and to prevent their making their way on board vessels lying in the port (same Report, p. 54). These measures, which are evidently of the highest possible importance, appear to have, in several instances, prevented plague from becoming established in our seaport towns.

(*b*) **Prevention of the Spread of Plague in an Infected Locality.**—When plague has once appeared in any inhabited place, measures are required to limit its spread, to prevent other persons from becoming infected, and to destroy, as far as possible, the active bacilli present, whether these are attached to the objects surrounding the sick, or in lower animals, especially rats. Formerly attempts were made to isolate the infection by shutting up the houses in which cases of plague occurred till all the inmates had either died or recovered. This was notoriously the method adopted in the old London epidemics, including the great plague of 1665. These measures were not only cruel, as involving the almost certain infection of most of the inmates in the affected house, but dangerous, as such a house was, by concentration, converted into a more virulent focus of plague than it was originally.

The measures now adopted, which were also recommended by the more enlightened sanitary authorities even in old times, aim at isolation of the disease by evacuation of the house, the inmates being conveyed, if already infected, to a hospital, or, if unaffected, to an observation hospital. The rules now laid down by the Local Government Board in this country require:—(1) Immediate notification, enforced under penalty, to the Medical Officer of Health, and by him to the Central Board, of every recognised (or suspected) case of Plague. (2) Prompt scientific diagnosis by bacteriological testing of material from such cases. To assist in the identification, arrangements are made by which such material may be sent by the Medical Officer of Health to the Central Authority for examination by experts. (3) The measures to be taken to prevent the spread of plague are, generally speaking, those available against the more ordinary epidemic diseases. "These include prompt removal of the sick persons to hospital and their isolation therein; the destruction or thorough disinfection of all infected articles, with the effectual disinfection also of the invaded dwelling-place; the keeping under observation during ten days, after detection of each plague case of all persons who have been in contact with the patient, and house-to-house visitation for the discovery of unreported or suspicious cases; the abatement as speedily as possible of all insanitary conditions in the locality which may tend to the spread of the disease; and, in the case of death, the prompt disposal of the corpse, with all due precautions against its becoming a source of infection." . . . "An essential measure of precaution, in view of the observed relation between plague in rats and plague in the human subject, will be the prompt destruction of all rats in districts threatened or invaded by plague, care being taken that their carcases are collected and burnt without being unduly handled" (94).

For the protection against infection of doctors, nurses, and others in attendance on the sick, or otherwise exposed to infection, the Board recommends the use of Haffkine's plague prophylactic, and is prepared to issue this material to the medical officers of health of districts actually invaded by plague.

For the disinfection of contaminated objects, and for floors, the Board recommends the solution of perchloride of mercury as generally used (common sublimate, half an ounce; hydrochloric acid, one fluid ounce, with five grains of aniline blue in three gallons of water), or 1 per cent solution of chlorinated lime, or 1 in 50 of formalin. For disinfecting the interiors of rooms chlorine gas is preferred to sulphurous acid; but spraying of a liquid disinfectant (as above) on the walls and floors is more efficacious. In a later report (1904) the Board gives the

results of examination by Dr. Haldane of the Clayton method for disinfecting ships and killing rats on board ship. This method is also applied to the disinfection of houses. It consists essentially in the combustion of sulphur at a very high temperature, producing not only sulphurous acid, but sulphuric anhydride and other sulphur products. This process has been carefully tested by Dr. Simpson, Dr. Hewlett, and others, and found to be the most satisfactory and efficient method for the purposes mentioned above (Simpson, p. 359, 391, etc.).

The regulations summarised above agree in the main with those carried out in all countries where plague has appeared, and in some places, as in Glasgow, with conspicuous success; but modifications are necessarily required by local circumstances. In the Indian cities popular opposition made it impossible to carry out such measures thoroughly.

In the Indian villages and small communities, a complete evacuation, with the removal of the population to temporary camps while their dwellings were being disinfected, was found to be very efficacious in checking epidemics, and was successfully carried out in the villages of the Punjab, by Captain James. Similar measures had, indeed, been adopted by the inhabitants of the Himalayan villages of their own accord. In Cape Town some plague-infected areas were completely cleared of their native population, who were provided with temporary dwellings in another quarter; and thus the plague was completely stamped out among the native population (Simpson).

For the destruction of rats, besides ordinary methods, the introduction by Danysz of a bacillus pathogenetic to them has been widely used for their destruction. In some places this method, of which the details cannot here be given, has been very efficacious; in other places much less so. Success appears to depend upon measures adapted to maintain the virulence of the cultures. It has been applied either by inoculating a number of rats, who are then set free to infect their brethren, or by distributing articles of food impregnated with the virus.

In the disinfection of contaminated objects, it has been shewn that exposure to abundant fresh air and sunlight are important adjuncts to all antiseptic treatment; and may indeed be efficacious without chemical aids, though requiring a much longer time.

All measures adopted to prevent the spread of plague are based upon the supposition that the disease is directly or indirectly communicable from the sick to the healthy; and though it has been shewn that the contagiosity, in the ordinary sense, of plague is very limited, it is better to proceed on the supposition that it may be thus conveyed. The difficulties raised by adopting this hypothesis are less important than the possible dangers of neglecting the precautions thus suggested.

There may be some doubt as to whether what are called ordinary sanitary precautions—cleanliness, attention to drainage, prevention of overcrowding in dwellings, etc.—have any great influence in limiting the spread of plague; but there can be no doubt that the neglect of these renders any inhabited place a favourable soil for the growth of the germs of plague; and that in places which exhibit some approach to "sanitary perfection" the disease is far less likely to establish itself.

J. F. Payne.

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J. F. P.

MALTA FEVER

By J. LANE NOTTER, M.A., M.D.

SYNONYMS: *Mediterranean fever; Gastric remittent* and *Bilious remittent fever; Mediterranean gastric remittent fever; La febbre gastro-biliosa; Fæco-malarial fever; Intermittent typhoid; Adeno-typhoid; Febris complicata; Febris sudoralis; Typho-malarial fever; Pythogenic septicæmia; Rock fever; Neapolitan fever; Danubian fever.*

Short Description.—An endemic fever of long duration (usually lasting from a few weeks to many months), accompanied by profuse perspiration and constipation, and often followed by pains of a rheumatic or neuralgic character, with swelling of the joints, orchitis, and tenderness and enlargement of the spleen. The disease is further characterised by a small mortality, tedious convalescence, a constant liability to relapses, and well-marked anæmia. The term "Undulant" fever was suggested by Hughes (11), but as Col. Bruce has shewn these undulations are merely recrudescences or relapses of the fever, which may occur, and often do, in enteric and other fevers.

History.—In the *Epidemics* of Hippocrates there are passages which, making allowance for the differences between the modes of thought and expression of his day and those of our time, might almost pass for a brief description of the disease.

The earliest mention of this fever is found in the reports of the medical officers of the navy and army in the early part of the last century. That it undoubtedly existed not only in Malta, but also in other parts of the Mediterranean, is very clear from these reports. Burnett, writing on the fevers of the Mediterranean in 1816, describes

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